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Editorial

Earlier dialysis and anabolic steroids in acute renal failure

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Acute reversible renal failure (often termed "acute tubular necrosis") is met with in many branches of medical practice. Of those patients referred to Leeds for treatment with the artificial kidney, approximately 50 per cent can be classified as surgical or traumatic, 30 per cent as medical, and 20 per cent as obstetric cases. Now that artificial kidney units are commonplace, there has been a rapid development of understanding of the uses and limitations of these machines, and this has increased rather than diminished the need for rational therapy in patients with this syndrome. The symptoms of uremia are due to the accumulation of the products of tissue breakdown, and treatment should therefore be directed to (1) the removal of these products by dialysis, and (2) the reduction of protein catabolism. In recent years there has been both a reappraisal of the time for dialysis, in order to control the uremia more effectively, and also of the methods available to reduce protein catabolism.

The trend at present is toward earlier and more frequent dialysis.[1-5] This is unnecessary in those patients with acute tubular necrosis who have a rate of rise in blood urea nitrogen of less than 30 mg. per cent per day. In these patients with adequate treatment, including the use of the artificial kidney when necessary either on clinical grounds or when the blood urea nitrogen reaches 200 mg. per cent, the recovery rate is more than 90 per cent.[6]

In regard to patients with a high rate of protein catabolism, in whom the blood urea nitrogen rises more than 30 mg. per cent per day, the results are far less satisfactory, and, on the basis of the above-mentioned criteria for dialysis, recovery occurs in only about 30 per cent of patients.[5,7] Acute renal failure in this group of patients is almost always a complication of surgical or accidental trauma, and similar low rates of recovery have been reported in other series among patients with traumatic renal failure.[7-10] The main cause of mortality in these patients is either the primary lesion (especially in the accidental trauma group) or complications related to the uremic state, particularly infection,[5,8,9] and these are the patients in whom the use of earlier dialysis results in improved survival rates. Daily dialysis[2] and continuous dialysis[3] require a great deal of equipment and staff, besides being more troublesome for the patient, and it has been shown that in this group of patients

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excellent results can be obtained by dialyzing when the blood urea nitrogen reaches 120 mg. per cent, that is, before the symptoms and signs of uremia develop, provided that a machine with a dialyzing surface area greater than 2.5 square meters is available. This technique results in a more balanced correction of the biochemical abnormalities, and usually allows at least two clear days between dialyses for attention to the other clinical needs of the patient.[5]

It is clear that mortality and morbidity can be reduced by more adequate control of uremia by dialysis in patients with a high rate of protein catabolism, but in either group of patients any measure which will reduce the rate of protein breakdown will prolong the time between dialyses and allow for mobility, physiotherapy, investigations, and other treatment. Theoretically, the rate of protein breakdown can be reduced in three ways: (1) by high caloric diets without protein, by mouth; (2) by 50 per cent glucose by caval catheter; and (3) by anabolic steroids.

The use of high caloric diets without protein has been advocated.[11,12] Fat is usually impracticable for this purpose because of the resulting nausea, vomiting, and diarrhea, and the risk of fat pneumonia in ill patients. Although carbohydrate is more satisfactory, its use is limited by the ability of the patient to tolerate oral hypertonic glucose, and its effect may be reduced by infection and tissue destruction.[13] The resulting depression of protein catabolism is, therefore, variable.[14] Thus, in practice, although this form of treatment is rational, it is frequently of only limited practicable value.[7,15,16]

Although the use of 50 per cent glucose by caval catheter has been fairly widespread in the treatment of acute renal failure, it has been shown that this has relatively little effect on the rate of rise in blood urea nitrogen.[17] The risks of this form of therapy, which include thrombosis,[18] perforation of the vena cava, infection, and immobilization,[19] usually outweigh its usefulness in most patients for routine use. It is possible that infusions of levulose may be preferable to glucose if this route has to be used.[20]

As far back as 1891, it was shown that an injection of an extract of rabbit testes caused a slight reduction in excretion of urea in two patients.[21] In animal experiments,[22,23,24] androstenedione and testosterone were shown to induce a prompt and sustained decline in excretion of urea, without elevation of the nitrogenous constituents of blood, and this appeared to be due to a general anabolic effect.[25] In uremic animals, treatment with testosterone propionate prolonged survival,[13,26] but was ineffective in nephrectomized animals which also had turpentine abscesses.[13] Early case reports appeared of a few uremic patients treated with testosterone,[27,28] but since then other workers have considered its usefulness to be limited both by its relatively small effect on protein catabolism and by the virilizing side effects.[15,29]

Recently, synthesis of several new steroids related to testosterone but with a greater anabolic/androgenic ratio has revived interest in the clinical use of such substances. These include norethandrolone, methandrostanolone, and nandrolone phenyl propionate. In patients with acute renal failure due to obstetric causes it has been shown that norethandrolone will reduce the rate of protein breakdown by 60 to 70 per cent, as compared with a 35 per cent reduction by testosterone propionate and methyl testosterone and a 23 per cent reduction by progesterone, although a combination of methyl testosterone and progesterone is as effective as norethandrolone.[30] In this series no patient with acute renal failure after pregnancy failed to respond to norethandrolone, and it was thought that this drug was perhaps more effective than other anabolic steroids in this group of patients. Similar results with norethandrolone have been found in some, but not all, patients of both sexes with acute renal failure due to other causes. Nandrolone phenyl propionate has also been shown to reduce protein breakdown by about 60 per cent in many cases of acute renal failure, but lack of response was again seen in some cases.[16]

With both these drugs the patients who showed little or no response are those with excessive protein catabolism due to infection, internal hemorrhage, or extensive tissue trauma. These patients—"hypercatabolic patients"—may fail to respond for

various reasons, perhaps because the anabolic steroid is incapable either of preventing breakdown of devitalized tissue or of accelerating anabolism of nitrogenous material other than that produced from normal cells. Another possibility is that these patients are under considerable stress and may well produce a large quantity of adrenal cortical hormones, which are known to be catabolic and have been shown experimentally to antagonize the effects of synthetic anabolic steroids.[31,32] The patients in whom anabolic steroids are of negligible value are, in fact, usually those in whom acute renal failure follows surgical or accidental trauma, and these are the patients in whom earlier dialysis is of such importance in reducing the mortality rate.[5]

At the start of the recovery phase from acute renal failure, patients are often malnourished, and this renders them particularly liable to infection, poor healing of wounds, and prolonged and difficult convalescence. It has been shown that patients treated with anabolic steroids during the uremic phase of their illness returned to nitrogen equilibrium far quicker than did corresponding patients who had been treated with glucose alone.[16]

The way in which the so-called anabolic steroids act is so far unknown. It is uncertain whether they are in fact anabolic or whether they may be anticatabolic in action, or perhaps both. In patients with acute renal failure after pregnancy the action does not seem to be related to androgenicity, because testosterone is much less effective than norethandrolone in these patients.[30] Unfortunately, similar experiments have not yet been carried out on patients with acute renal failure from other causes, and in particular in male patients. Neither is the action of these steroids related directly to their progestational properties, for, although progesterone has been shown to be anabolic in two patients with acute renal failure after pregnancy,[30] progesterone and related steroids with a β-orientated side chain at C_{17} are usually catabolic.[33] It is possible that the greater effectiveness of norethandrolone in patients with acute renal failure after obstetric accidents may be due to its progestational activity, but nandrolone phenyl propionate, which has no progestational activity, is probably as effective as norethandrolone in patients other than those with acute renal failure after pregnancy.

Anabolic steroids have a relatively rapid action on protein catabolism; the full effect is seen within 24 hours after administration is started.[30]

The side effects of treatment with anabolic steroids include virilization and the development of jaundice, but since treatment for acute renal failure is for only a short time, these are unlikely to be of significance. We have seen transient hypercalcemia in one patient who had traumatic uremia with multiple fractures, while being treated with norethandrolone during the early recovery phase. This may resemble the hypercalcemic syndrome with nephrocalcinosis which has been reported in patients who had osteolytic bone lesions and were immobilized while receiving androgens and estrogens.[34]

The use of anabolic steroids in acute reversible renal failure can be justified on three grounds.

1. If by their use the rate of protein breakdown can be reduced so that the rate of rise in blood urea nitrogen is less than 30 mg. per cent per day, it is probably necessary, generally, to dialyze these patients only when signs of clinical deterioration begin to appear, and more cases can be managed without the need for dialysis. Even if this is not possible, if the rate of protein breakdown can be slowed at all, fewer dialyses will be required, so that fewer blood vessels need be sacrificed and more time will be available for mobility, physiotherapy, investigations, and any other necessary treatment.

2. It seems probable that the effect of calories in depressing protein breakdown is relatively insignificant in comparison with the effect of anabolic steroids. Because many patients find the toleration of hypertonic glucose by mouth difficult, it would appear that, if such patients are given anabolic steroids, the glucose could be replaced by more palatable fluids. It may even be possible to give patients protein,[35] possibly in the form of milk or synthetic amino acids, in order to assist protein anabolism. Animal experiments have suggested that l-lysine may be useful.[36]

3. There is no doubt that during three

or four weeks of oliguria on a low-protein diet these patients suffer from progressive and extreme starvation. Undoubtedly, this must contribute to the mortality and morbidity which occur during the recovery phase from acute renal failure. Therefore, any treatment which conserves body protein will be of value in preventing the occurrence of late complications while also shortening the period of convalescence which these patients require.

In light of the foregoing, it would seem reasonable to use the newer anabolic steroids routinely in the management of all patients suffering from acute reversible renal failure.

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Special report

Einthoven Symposium*

Opening remarks by Professor Dr. H. A. Snellen

Ladies and Gentlemen, it is a very great pleasure indeed to welcome you all at this symposium in honor of the centennial of Willem Einthoven on behalf of the organizing bodies: the University of Leiden, which can be proud to have had Einthoven among its professors for more than forty years, the Boerhaave organization for postgraduate teaching, the Dutch Physiological Society, and the Dutch Cardiological Society. I feel privileged to call on our Dean of the Medical Faculty, Professor Gaillard, to open this symposium by saying a few words to us.

Opening words by Professor Dr. P. J. Gaillard

Ladies and Gentlemen, it is a great pleasure and honor to open the symposium. As Dean of our faculty, I welcome all participants and guests on behalf of the faculty of which Willem Einthoven was such an outstanding member.

Those who remember Einthoven know that he thought as a sage and at the same time felt as a man. As young students we often hesitated to approach him, but once we did, we always became impressed by his charm and by the fatherly way in which he formulated his advice.

Therefore, you will understand that we feel proud and happy that this symposium is going to be held in commemoration of him.

I wish you a most successful and profitable day, guided by the spirit of the man to whom we attribute our highest feelings of admiration.

With these few words, Ladies and Gentlemen, I declare the session open.

*Proceedings of the Symposium in commemoration of the birthday (May 21, 1860) of Willem Einthoven, held in Leiden, Netherlands, on Saturday, June 25, 1960, under the sponsorship of the University of Leiden and the Dutch Physiological and Cardiological Societies.

Developments in the physiology of color vision since Einthoven

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In the nineteen-twenties the necessity for a more rigid base for photometric brightness and color specifications and for the development of color reproduction greatly stimulated the development of more systematic research programs in color vision.

Since then there has been an increasing tendency to collect data about behavioral functions along a scheduled line by a group of investigators often from different specializations, rather than progress being made more exclusively and more incidentally by the ingenuity and many-sidedness of individual persons. Einthoven stands as a representative and as a vivid example of the latter class of individuals just at the transition to this new look in scientific activity.

Since his death an enormous amount of accurate data on color vision functions has become available. Improvement in technical equipment has made a vast contribution to this progress. This is particularly evident in the case of the handling and measurement of spectral energy distribution and of electrical phenomena in neurophysiology, which nowadays can be done relatively easily and accurately with the aid of recently developed laboratory equipment.

However, with respect to what previous generations had already discovered or had already thought of, little progress has been made in so far as essentially new ideas are concerned.

The highlights in the historical development of the physiology of color vision since Einthoven can be discussed under three headings. In the first place there is the discovery of what I like to call two retinal directional effects.

In 1933, Stiles and Crawford from the Photometric Division of the National Physical Laboratories in London found that the color receptors in the retina—the cones—have a sensitivity that depends on the direction of the incident light. The same workers found in 1937 that this directional effect was also influenced by the wave length of the light. In 1937, Stiles also published extensive measurements he had made of another effect: it appeared to Stiles and Crawford that the apparent color also depends on the direction of the light incident upon the retina. Hansen from the Zeissworks mentioned that he had noticed this effect in 1929. Actually, it is very surprising that these effects remained hidden until the nineteen-thirties.

Indeed, the influence that the eccentricity of the light falling on the pupil has on apparent brightness and on apparent color is far from small. On the average, all through the spectrum for photopic vision in the fovea, sensitivity is about 4 times less for light coming 3-5 mm. ec-

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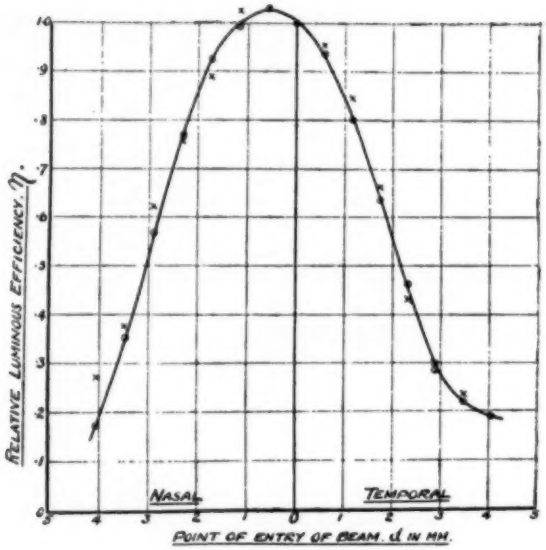

Fig. *1*.

centrically through the pupil than it is for light passing centrally (Fig. 1). This decrease in sensitivity goes with a change in apparent color that covers, for the bluish-green part of the spectrum, as much as 10 mμ (100 Ångström) (Fig. 2). People with normal color vision can distinguish between wave lengths only 1 to 2 mμ apart in this region of the spectrum.

Einthoven and also Brücke came close to the discovery of both these effects when they studied the effect of chromastereopsis as described by Donders. In this study, Einthoven moved stenopaic diaphragms in front of the pupils. He demonstrated with this that for suitable positions of the stenopaic diaphragms, the selfsame observer can see the red in front of blue as well as the reverse.

Recently, Vos pointed out and reported at the September, 1959, meeting of the Dutch Physiological Society that a reversed chromastereoscopic effect can be obtained as well when the preferential direction of the cones is eccentric as compared with the axes of the eye. Probably, eccentricity in pupil position and in directional preference of the cones contributes equally to the reversed chromastereoscopic effect.

Anyhow, Einthoven's experiments with different locations of stenopaic diaphragms in front of the pupil when looking at objects of different colors represents the situation in which the Stiles-Crawford effects most easily reveal themselves.

Recently, Campbell discovered a third retinal direction effect. It refers to the dependence of visual acuity on obliqueness of the light and can be left out of consideration here.

I now come to the second highlight in the development of the physiology of color vision in the last decades. It refers to the theory of color vision. A good many of the outstanding research workers share the opinion that almost all facts of color vision point to the necessity of accepting the existence of three fundamental response systems at the receptor level, of which the spectral sensitivity curves are very similar or equal to those proposed by Pitt. The basis of this view became even more firmly established when we recently succeeded in bringing both Stiles-Crawford effects under one explanation.

In this study, the results of which were also reported by Walraven at the September, 1959, meeting of the Dutch Physiological Society, Pitt's set of curves was involved. I will not repeat fully the train of thought but considerable help came from Stiles' own speculations on the basis of his discoveries as well as from Brindley's

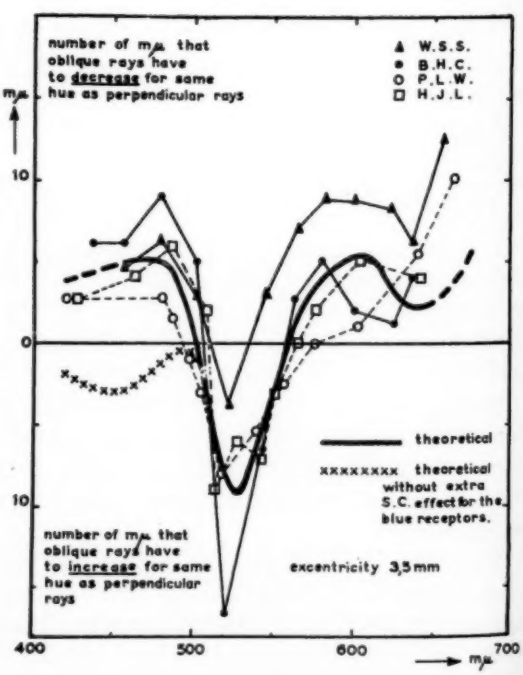

Fig. *2*.

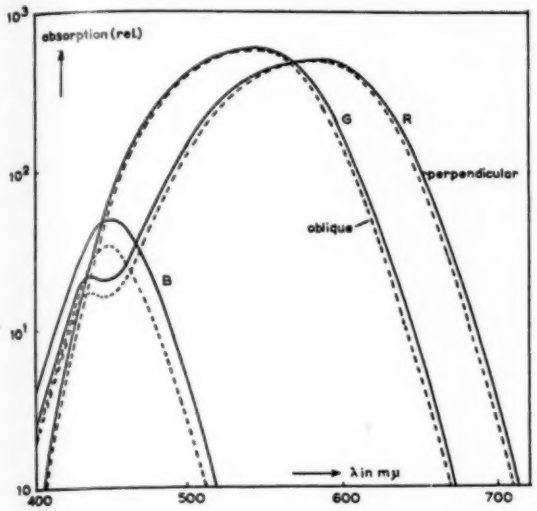

Fig. 3.

work on the change of color equations for different eccentricities in the pupil. From this was developed the idea that, in the outer segment of the cones, with increasing obliqueness of the light an increasing fraction of the light leaks away to the surrounding tissue and does not further contribute to the perception. Simplified, it means a shorter effective pathway through the receptor for oblique light. In the case of high concentration of the photopigment, shortening of the pathway narrows its spectral absorption curve (Fig. 3).

For acceptable values of absorption power for perpendicular entrance of the light at the maximum of the spectral absorption curves both Stiles-Crawford effects were quantitatively explained. My belief is that this result is a very important one in favor of Young's idea of three types of color receptors in the fovea.

Although most contemporary theorists now agree that the color vision system is based on a three-variables mechanism, dissident opinions frequently are expressed. By and large these suggestions stem from the Hering opponent-colors theory. However, this theory itelf also contains a three-variables mechanism, the components being the antagonistic red-green, yellow-blue, and black-white systems.

An increasing amount of experimental data makes it probable that the Young-Helmholtz and the Hering theory refer each to a single zone in the chain of events involved in color perception. This idea of more than one zone of activity came from Donders.

I shall mention briefly some of these experimental data. First of all, there is the work of Rushton. He could prove the existence of photopigments by making measurements of the spectral reflectance of the retina under different conditions of adaptation obtained by strong illumination with light of different colors. The changes he found in spectral reflectance are due to the bleaching of the visual pigments by the strong illumination. The spectral sensitivities which he deduced for the pigments from these measurements are very much similar to Pitt's curves.

Another important contribution came from Granit, who, with microelectrode techniques, measured the electrical activity of retinal elements. Elements of different spectral sensitivity curves were found pointing to the existence of different response systems in the retina. This work is so generally known that there is no urgent need for extensive reporting of it here. His modulators represent the Young-Helmholtz type of receptors. His dominator is an example of a mechanism that is more of the Hering type, a brightness mechanism.

Sveatichin recently found such a dominator also in the retinae of fishes. The most remarkable point in his work, however, is that he also found nerve elements in these retinae, with a spike activity exactly representing Herings' antagonistic color components. He used microelectrode techniques. Some nerve elements in his work demonstrated in some regions of the spectrum a positive electrical activity, and in other regions, a negative activity. What type of nerve elements they were is not exactly known; at least some disagreements of opinion are not yet solved. Anyhow, this type of elements is found and does exist in the retinae of fishes. It might be that this phenomenon is strictly related to the existence of twin cones in these retinae.

It is encouraging that some of the most outstanding theorists—such as Judd, for instance—are convinced now of the possibility of integrating Hering's and Young-Helmholtz's hypotheses on the basis of three-variables mechanisms in some type

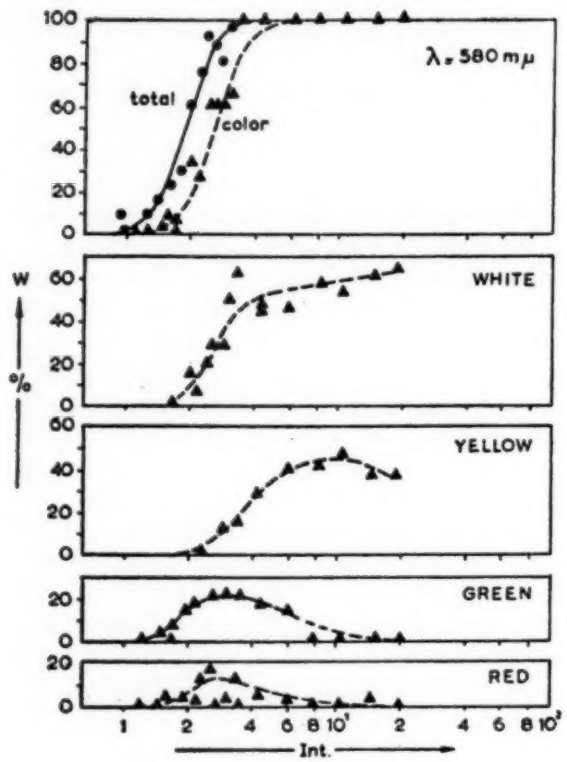

Fig. 4.

of zone theory. For instance, it has been shown by Judd that Müller's zone theory is quite consistent and can be used to explain a good many of the facts in color vision.

The third main point to which I would like to draw your attention is also theoretical in nature. Around 1900, Planck made the final discovery of the corpuscular nature of light. It was not until 1915 that it was asked whether and how in the physiology of the visual system this quantum nature is revealed. Mutual discussion between Lorentz and Zwaardemaker resulted in Zwaardemaker's speculative suggestions that the active energy needed in order to reach the threshold is fulfilled for the nervous system when two quanta are absorbed. In 1944, this hypothesis was given a more substantial foundation by van der Velden with the aid of ingenious theoretical statistical considerations and with related experiments to back them up. The basic idea of this quantum theory in vision is that statistical fluctuations in the flux of quanta are apparent in perception and are reflected in the threshold mechanism.

As a result of the work of van der Velden and others it became a generally accepted fact that a rod is activated by the absorption of one quantum. The same can be concluded for the cones. Two such absorptions sufficiently close together in time and space result in a perception. Although these more precise threshold conditions are considered by some authors to be rather speculative and not very well established, others have proceeded along the lines suggested by quantum theory for further development of these ideas. Recently, it was proved that an analysis of the instability in color identification near the threshold of vision is possible in terms of the quantum theory (Fig. 4). Walraven reported work on this subject in the June 1958 meeting of the Dutch Physiological Society. It was found that a twofold coincidence of quanta in the cones does not always result in a color perception. It frequently produces only an achromatic sensation. In the red the mechanism responsible for a red appearance starts to work in a twofold coincidence basis (Fig. 5).

Some more considerations of this type were abstracted from the experiments. Quantum theory has already been applied for the description of various visual functions, like threshold dependence on size and exposure time, and on velocity in the case of a moving target. It also described the dependence of visual acuity on brightness, and, furthermore, it has been extended by de Vries and Rose to explain the dependence of contrast threshold on brightness. It is worth while to consider this point a little further. It was suggested by de Vries and Rose—and this was confirmed by earlier experiments—that differences in apparent brightness occur when physically

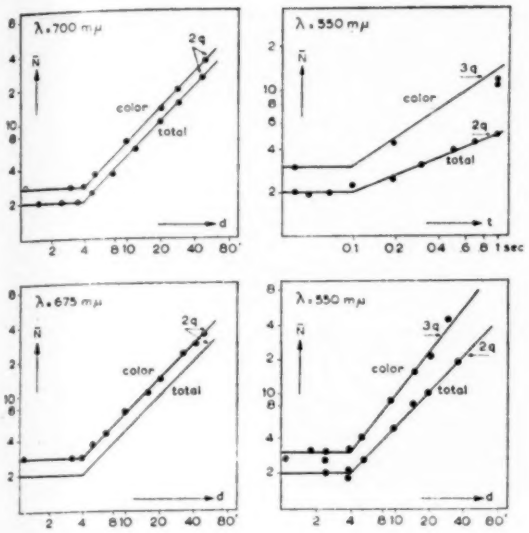

Fig. 5.

the difference between the intensities is significant. It means that the intensity difference between the stimuli must exceed the statistical differences in the quanta numbers between both.

Very recently, we tried to describe also just noticeable differences in color on similar assumptions. It proved that color vision functions in such a simple case as tritanopia can easily be explained in this way. The base for this argument is that two stimuli can be distinguished when the collections of statistically possible combinations of quantum numbers absorbed in the three color receptor systems, n_r, n_g, n_{bl}, do not overlap. Again, Pitt's fundamental response curves were taken as a basis for the three receptor systems.

At least quantum theory might prove to have the same merits as the photochemical theory proposed and developed by Hecht (1937). This theory kept researchers working on systematic projects for some time. However, it is not hoped that the criticism that can be leveled at Hecht's photochemical theory never can be applied to quantum theory. I point here to the very fact that before Hecht expressed his theory, the basis of it could already be considered as being disproved. Indeed, Zwaardemaker and Lorentz found before 1919 that very few quanta are involved in the visual process, and that these few, moreover, are distributed over several receptors. In that case, application of the mass-action law for chemical reactions to the photochemistry in the receptors is of little value. Hecht himself (1942) became also the first pioneer for the "quantum type" of approach in visual theory in 1940.

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Ion movements underlying the cardiac action potential

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The years of 1902-1903 are marked by Einthoven's publication[1] of the first surface electrocardiograms which, for all practical considerations, may be called undistorted (Fig. 1). Before and after this date it has been recognized that the electrical variations recorded from the surface of a body are composite in nature. Consequently, much effort has been made to obtain the potential-time course from the site of its origin: the surface membrane of cardiac fibers. In 1883, Burdon-Sanderson and Page[2] were leading off between an injured and a noninjured spot of the frog or tortoise heart and obtained the first "monophasic" records by means of a fast moving capillary electrometer. Such tracings are currently interpreted to reflect the variations taking place in the intact part of the heart; it is assumed that the damaged region makes no contribution. Schütz, in 1929, found the means to keep one spot injured "permanently" by the combined effect of a ligature and suction. This technique made it possible to obtain reproducible records over longer periods of time and gave rise to systematic investigation of the monophasic action potential under a variety of conditions.[3]

The recording of membrane potentials

It was in 1949, when the problem of the recording of potentials was brought one step further. Ling and Gerard[4] described their microelectrodes which could be inserted into the inside of a single muscle fiber, thus making possible the recording of a potential difference across the surface membrane, *the transmembrane potential.* The lower half of Fig. 1 illustrates the procedure and results. With the tips of two microelectrodes on the heart surface a "reference potential" is first recorded. One of the two electrode tips (diameter about 0.2 μ) is then pushed into a single fiber (diameter about 16 μ in mammalian heart). The potential jumps to a new steady value. This indicates that, during diastole, the inside of every fiber is negative by about 90 mV. with respect to the fiber surface: *resting potential.* When the heart is stimulated, a monophasic *action potential* results. To illustrate the temporal relationship with the surface electrocardiogram, the upstroke of the monophasic curve has been made to coincide with the beginning, and the downstroke with the end, of the ventricular complex (Q and T, respectively). The changes in potential that can be obtained at the level of a single fiber are about 100 times larger than those present in a surface ECG. It is noteworthy that during the first phase of activity the monophasic curve "overshoots" the reference line. This means that the inside of single fibers becomes positive with respect to the outside. It should be added—even in a talk given at Leiden—that this phenomenon was first

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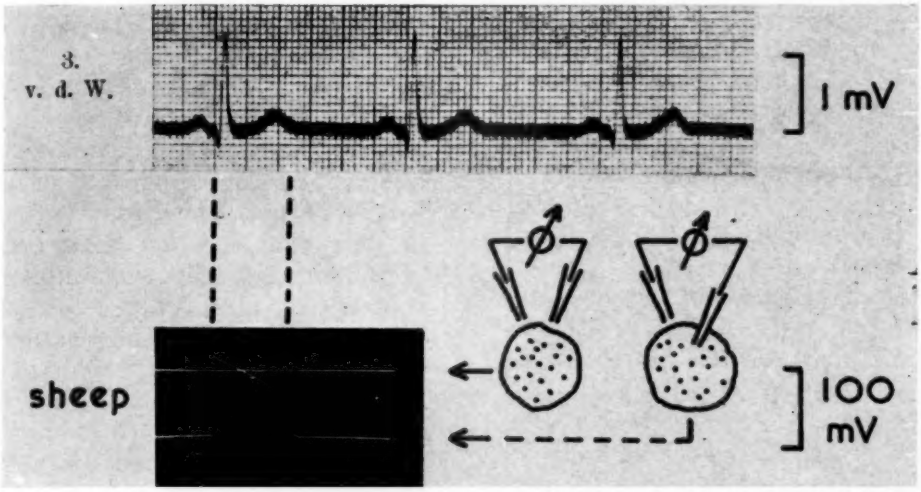

Fig. *1. Upper record:* Electrocardiogram of subject v.d.W., taken with Einthoven's string galvanometer, published in 1903. Time marks are 40 msec. apart. *Lower record:* Transmembrane action potential of a sheep myocardial fiber. The two records have been arranged so as to make the upstroke of the transmembrane action potential coincide with the Q wave, and the downstroke with the T wave, of the electrocardiogram.

described by Engelmann, Nuel and Pekelharing,[5] working at Utrecht. They were leading off between a noninjured and an injured spot and making contact with a slowly moving galvanometer, for short periods at different phases of activity. With a resting heart the galvanometer moved in one direction; in the beginning of cardiac activity the galvanometer moved "appreciably in the other direction."

At this point it seems appropriate to show a record correlating the electrical and the mechanical activity. In Fig. 2 the electrical record was obtained with a Ling-Gerard electrode, the mechanical record (from a whole turtle ventricle) by making use of a mechano-electrical transducer (RCA 5734). In cooled turtle hearts the action potential resembles a square pulse. Mechanical shortening starts shortly after depolarization; relaxation starts with a sharp "kink" when the membrane repolarizes.

The distribution of ions

Ionic order (Fig. 3) represents stored energy. Ion gradients make it possible for strong membrane currents to flow during certain phases of activity, whereas metabolic energy will be required during other phases of the cardiac cycle to reestablish the ion gradients.

According to analytical data, potassium ions are accumulated in the cardiac myoplasm by a factor of about 30, whereas sodium ions are present at a concentration 10 times lower than in the interspace (see Reference 7).

Little quantitative information is available on the rate of exchange of ions between the inside of cardiac fibers and their environment. The half-time for potassium exchange, as measured by the aid of tracer K, is of the order of 1 hour. As to sodium, there is evidence to suggest that

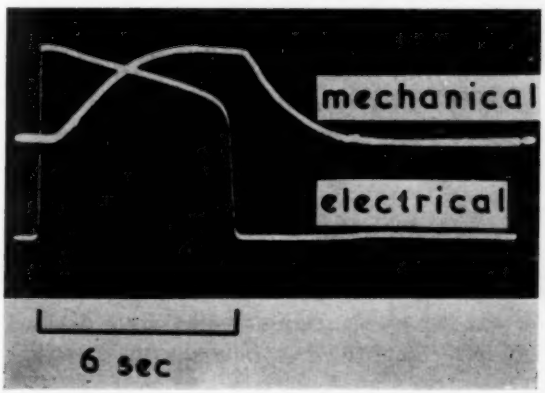

Fig. *2.* Temporal relationship between monophasic action potential and contraction. Turtle heart at 8°C. The upstroke and the downstroke of the action potential are retouched. From Weidmann.[6]

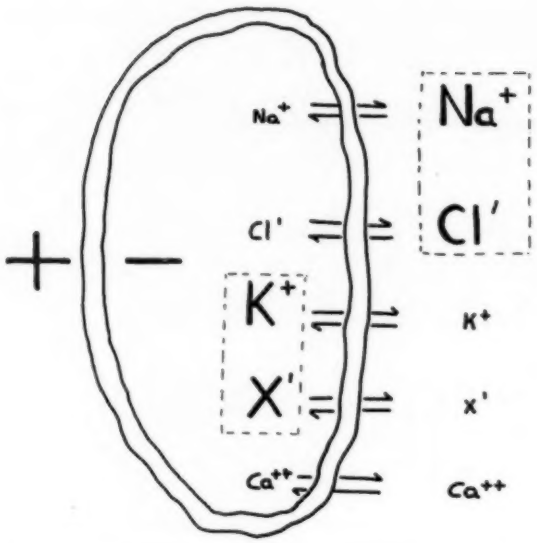

Fig. 3. Distribution of ions between the intracellular and extracellular spaces. The intracellular anions are not fully identified, and are therefore denoted by X'. Concentration ratio and half-time for tracer exchange (minutes), respectively: Na^+, 1:10 and 170; Cl', 1:30 and (?); K^+, 30:1 and 60; Ca^{++}, 3:1 and (?).

the permeability of the surface membrane at rest is lower than that to potassium ions, both from electrical data[7] and from tracer measurements.[9] Electrical data also suggest that the chloride permeability of the resting membrane is low as compared to the potassium permeability.[10,11]

Sodium ions have to be extruded from the fibers against both a concentration gradient and an electrical gradient. For thermodynamic reasons, this must depend on metabolic energy. Accumulation of potassium may, for theoretical reasons, be a "passive" process, depending on the voltage gradient established by sodium extrusion; but it is questionable whether or not a large proportion of potassium inflow depends, as shown for nerve fibers,[12] on the availability of metabolic energy.

Ion movements during activity

Nerve physiologists have, since the end of the second World War, made an important contribution to physiology as a whole by identifying the ionic species that are shifted between the intracellular and extracellular spaces in different phases of the action potential.[13] The results may be summarized by saying that an influx of Na^+ ions is responsible for the upstroke of the action potential (depolarization and "overshoot"), whereas a net outflux of K^+ ions brings about repolarization. Cardiac electrophysiologists have been busy testing how far the results obtained on peripheral nerve fibers are applicable to the heart.

It was noticed already by Overton,[14] in 1902, that the frog heart becomes unexcitable when the extracellular concentration of sodium drops below 10 per cent of its normal value (substitution of NaCl by saccharose). More recent experiments have confirmed this finding for sheep and calf myocardium.[15] Furthermore, the electrical changes observed (Fig. 4) are in agreement with the hypothesis that the membrane at rest is sparingly permeable to sodium ions, but undergoes an important increase in permeability when activated. If part of the NaCl is replaced by choline chloride (choline being a nonpenetrating ion), there is (a) no change of the resting potential, (b) a decrease of the "overshoot," (c) a decrease in duration of the action potential, and (d) a decrease in the upstroke velocity of the action potential (not seen in Fig. 4).

The view that repolarization in cardiac muscle is due to an increased outward movement of potassium ions is supported by tracer data. Fig. 5 shows the ^{42}K outflux from the coronary system of a turtle heart which had previously been "loaded" with ^{42}K. The curve has been corrected for the travel time in the vascular system

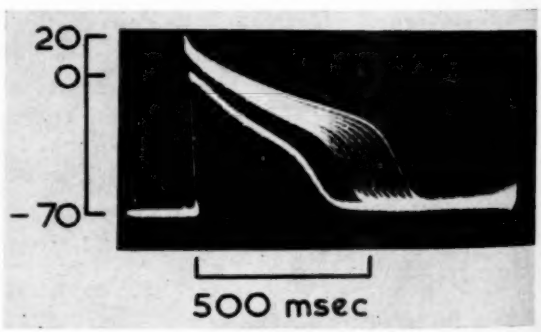

Fig. 4. Effect of substituting choline chloride for 80 per cent of the NaCl. Successive action potentials of the same ventricular fiber of a sheep heart. The camera was opened during the first 30 sec. of perfusion with the sodium-poor solution, then again between 60 and 90 sec. Upstrokes of the superimposed action potentials have been retouched. From Délèze.[15] (By permission of American Heart Assn., Inc.)

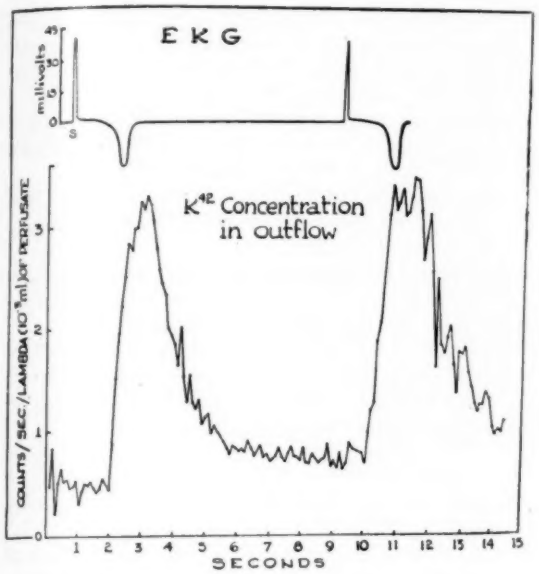

Fig. 5. Rate of outflow of ^{42}K from a turtle ventricle in the course of two heartbeats. From Wilde.[16]

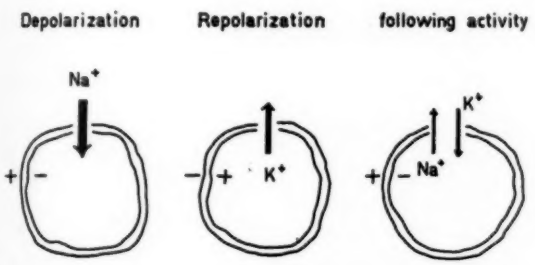

Fig. 6. Movements of ions in different phases of the action potential.

as well as for changes in rate of flow during contraction. It shows (a) that there is ^{42}K outflux even from the resting heart, and (b) that there is a large increase of ^{42}K outflow synchronous with the T wave of the electrocardiogram, i.e., synchronous with the phase of repolarization of the monophasic action potential.

The ionic movements are summarized in Fig. 6. Inward current of positive charge (sodium ions) causes depolarization, and outward movement of positive charge (potassium ions) causes repolarization. These currents result in a slight increase in the intracellular concentration of sodium and a corresponding decrease in intracellular potassium. In the turtle heart the loss of potassium ions associated with a single beat is estimated at 1/400 of the total intracellular content.[16] To keep the system in equilibrium, the ions exchanged during the action potential have to be "pumped" back, and it seems reasonable to assume that this happens mostly during diastole.

The experiments presented so far indicate that, qualitatively, the cardiac action potential can be explained on the same basis as the nervous action potential. Nevertheless, there is an important difference of a quantitative nature: activity in nerve lasts for less than 1 millisecond, whereas the action potential of a mammalian ventricle has a duration of 200 to 300 milliseconds. The simplest way to account for the difference is to assume that the permeability to potassium of the surface membrane rises rapidly when nerve fibers are depolarized but rises with a considerable delay when myocardial fibers are depolarized. Measurements of the electrical resistance of the surface membrane would agree with this hypothesis, for it can be shown that throughout the myocardial action potential the resistance is high, indicating a low permeability to ions.[17]

Concluding remarks

Looking at the results obtained during the past decade, we may say: (1) The absolute values of the cardiac resting and action potentials have been determined with a fair amount of accuracy, thanks to the microelectrode technique. (2) Reasonable interpretations have been made to correlate the measured membrane potentials and the data on the distribution of ions. (3) In a qualitative way, electrical activity in heart tissue seems to occur on the same basis as that in nerve tissue. (4) The data on the movements of ions in the heart are scarce so far, and much remains to be done until the cardiac action potential can be accounted for, in a quantitative way, in terms of ionic currents.

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The electrocardiogram in normal and some abnormal conditions

In revived human fetal heart and in acute and chronic coronary occlusion

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Nearly 55 years ago a telephone wire connecting Einthoven's laboratory with the internal clinic, made it possible to register electrocardiograms from patients. After some time this connection was severed by the clinician. It must have been a strange idea indeed that a machine could give information about the patient not detectable from direct contact with the patient. In many respects this interruption may be considered a symbolic action. Electrocardiography as a part of physiology, and electrocardiography as a part of clinical medicine had to go a separate way for a long time before reunion took place.

The group I represent here is nearly completely composed of persons interested in clinical medicine. Our work started in 1947, with the study of the transmural and intramural potentials in the dog and the goat. But our main target, the human heart, was not accessible. Only in the last year did we find a method suitable to investigate the exposed heart of the human being in a satisfactory way.

Experimental approach

A. Heart. The explorer of the electrical aspects of the heart is faced with many difficulties. How can he accomplish his main purpose, the unraveling of cardiac excitation, in such a way that his approach does not change the phenomena he wants to investigate? Two lines of approach are possible. One means is exposition of the heart by thoracotomy. Probably the complexes registered from the exposed heart are not identical with the complexes from the heart in the intact thorax. The second approach is the Langendorff perfusion of the isolated heart, a method which for the human heart was used for the first time by Zbyszewski[1] and perfected by Boden and Neukirch.[2]

B. Electrodes. Three kinds of electrodes were used. (1) Differential electrodes to record local phenomena. This type of

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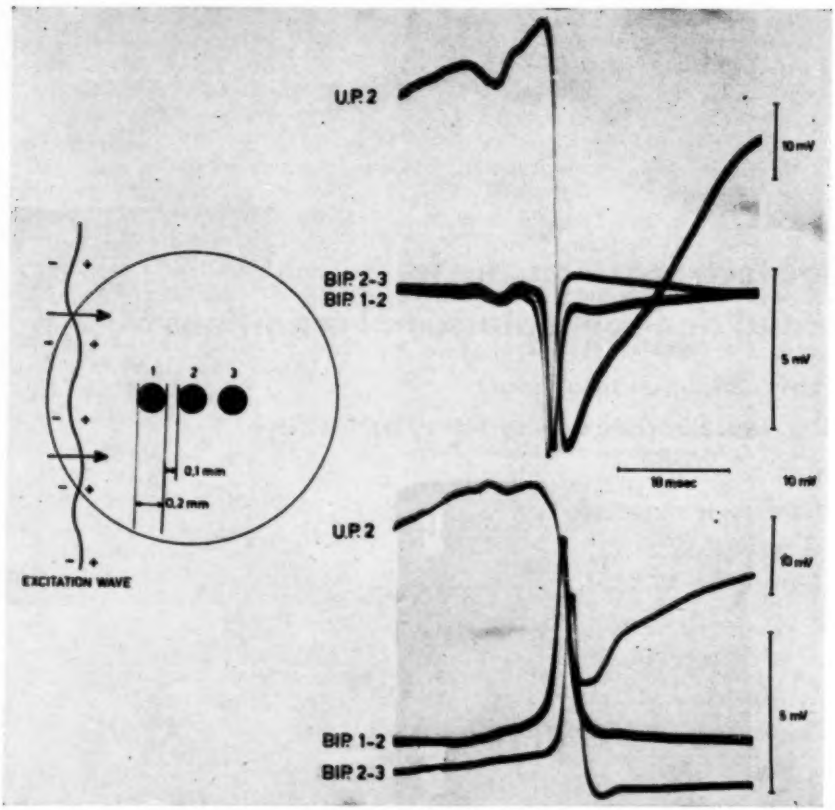

Fig. *1*. Three terminals, *1*, *2*, *3*, a distance of 0.1 mm. apart, were placed on the epicardial surface of the heart, in a region in which the excitation wave progresses from terminal 1 to 3. A point on the fast portion of the intrinsic deflection in unipolar complex from the middle terminal coincides with the point of intersection of the bipolar complexes.

electrode consists of two electrodes lying very close together, for example, 0.1 millimeter apart. (2) Small tipped unipolar electrodes for extensive exploration of the epicardial and endocardial surfaces of the heart. (3) Intramural needle electrodes.

Apparatus. A four-channel high-fidelity oscillograph with separate recording and viewing tubes was used.

Intrinsic deflection and local excitation. Our previous investigations[3,4] have shown that the electrical effects of local excitation can be best studied by means of differential electrodes. It can be demonstrated, however, that the electrical effects of local excitation can frequently be discovered in the unipolar records. A differential electrode with three terminals at a distance of 0.1 millimeter was placed on the epicardial surface on an area where the excitation process spreads from 1 to 3 (Fig. 1). The complexes between 1-2 and 2-3 are very similar. The intersection of bipolar complex 1-2 with complex 2-3 signals the arrival of the excitatory wave at terminal 2, coinciding in the unipolar record with a point on the rapid part of the intrinsic deflection. For the measurement of time relations, only the rapid portions in the complexes are used.

Contrary to the opinion of some investigators, we found that the location in the QRS complex of the electrical effects caused by local excitation is not constant. It may differ in complexes from different areas of the heart (Fig. 2). The effects of local excitation are represented by a fast deflection which may occur near the middle of the downstroke of the R, near the top of the S. On the ascending limb of the S it may appear as a negative going potential. In some areas, mainly on the posterior wall, we even found the effects of local excitation on the ascending limb of the Q.

Total excitation of dog heart

Total excitation of the heart of the dog, the experimental animal commonly used, is now rather well known.[3,5-7] I will comment on only a few points. During the study of the sinus node and A-V node, we were impressed by the sensitivity of these structures to pressure of the exploring electrode. Even slight pressure on the sinus node caused disappearance of the multiphasic electrical activity, specific for these structures. The introduction into the sinus node of a needle electrode of the type we used caused a complete disappearance of multiphasic activity.

Specific tissues of heart. The electrical activity of the main branches of the bundle of His can be seen as multiphasic deflections preceding the cavity potential.

The pattern recorded in the subendocardial branches of the Purkinje system is somewhat different; mostly only one or two spikes are found. We could find no appreciable delay between the spikes caused by activity of the Purkinje fiber and the beginning of the myocardial depolarization complex after the Purkinje depolarization.

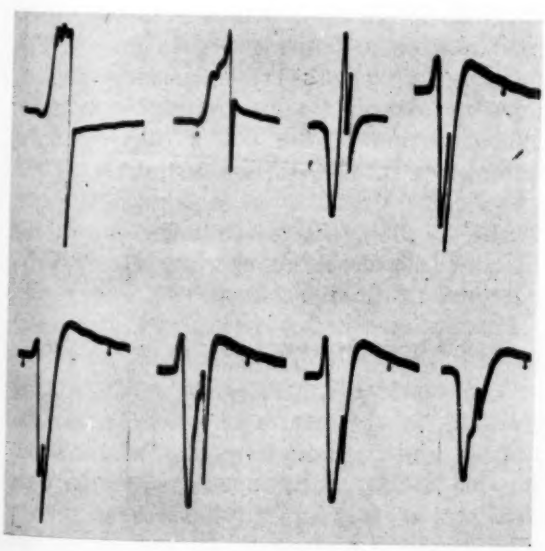

Fig. 2. Different locations of intrinsic deflection in QRS complexes. Unipolar complexes from different regions of the revived heart of a 7-month-old human fetus. The effect of local excitation can occur in the downstroke connecting top R with nadir S, near the top of the S, on the ascending limb of the S and ascending limb of a QS complex registered from the posterior side.

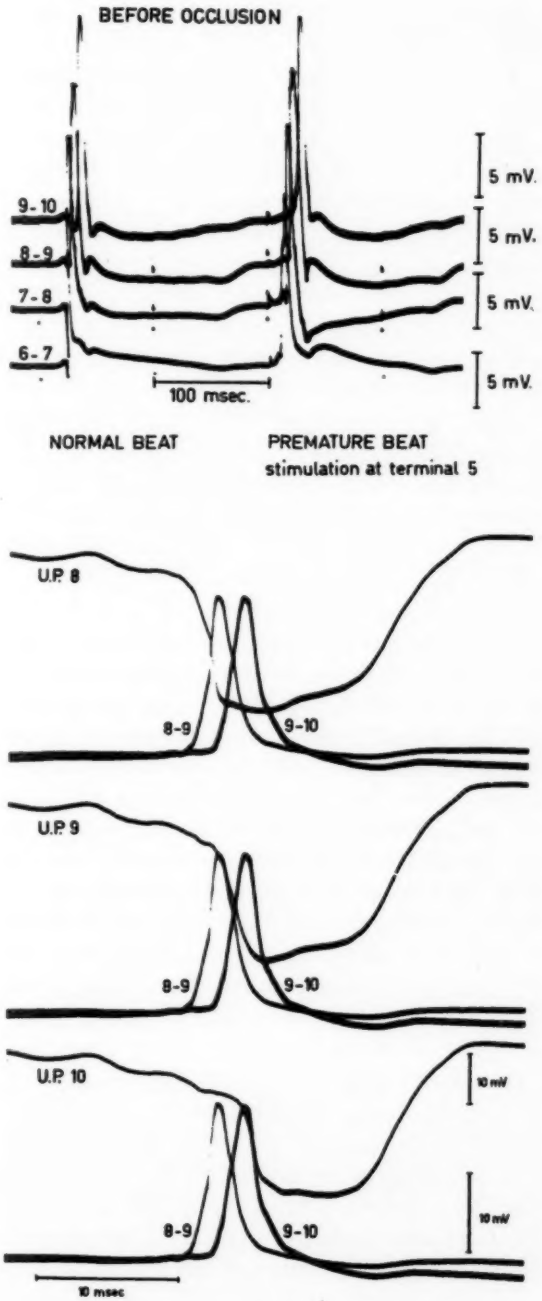

Fig. 3. *Top:* Bipolar complexes during normal beat, followed by premature beat caused by stimulation of terminal 5, situated in the subendocardial layer. *Bottom:* Bipolar complexes in outer layers of ventricular wall with unipolar complexes from the terminals between which the bipolar complexes were recorded. The intrinsic deflection in unipolar complex 8 is synchronous with the fast portion in upstroke of bipolar complex 8-9. In unipolar complex 9 the intrinsic deflection is synchronous with the intersection of the downstroke in 8-9 and the upstroke in 9-10. In unipolar complex 10 the intrinsic deflection is synchronous with the downstroke in 9-10. The duration of the bipolar complexes is approximately 5 milliseconds.

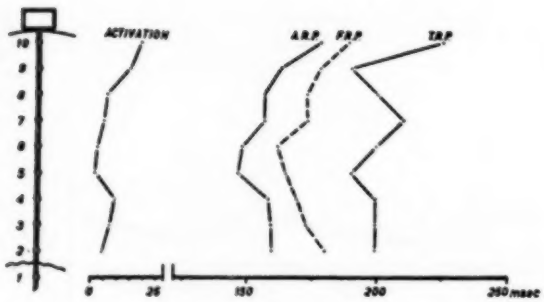

Fig. 4. The time of activation in the intramural layers was measured by the time of occurrence of the intrinsic deflection in unipolar and bipolar records. *A.R.P.* is the absolute refractory period. *T.R.P.* is the total refractory period, the duration until cardiac excitability has regained the diastolic level. *F.R.P.* is the functional refractory period, the period after which the myocardium is capable of conducting a propagated excitation wave. The time course of F.R.P. rather closely follows activation time.

The Purkinje system distributes the excitatory wave in 5 to 10 milliseconds to all subendocardial parts of the ventricles.

The question of the presence of intramural extension and the degree of intramural extension of the Purkinje network is not solved. In previous experiments, we gave only indirect evidence for the existence of an intramural network of the inner layers of the ventricular wall in the dog. For many years we looked for evidence of electrical activity of the Purkinje system in the left ventricular wall, but never found it. We did find it, however, in the goat. Here we could record Purkinje activity preceding the muscular depolarization complex in bipolar intramural records at different intramural layers, even in the subepicardial layers. The intramural extension of the Purkinje network is proved conclusively by Meyling and Ter Borg.[8,9]

Intramural excitation. In the outer layers of the ventricular wall the excitatory process progresses with nearly constant velocity, approximately 50 cm. per second, toward the epicardial surface. The region in which depolarization takes place appears to be very sharply defined. The electrical effects caused by this wave can be represented by a polarized surface. The distance between sources and sinks is 1 mm. maximum. The drop in potential across this wave is at least 15 mV. (Fig. 3).

Ventricular septum. The ventricular septum is activated from both sides.[10-12] No functional boundary between the portion supplied by the right and left bundles can be demonstrated.[10] The basal regions of the septum are activated latest in the cardiac cycle; therefore, the excitation wave in the ventricular septum progresses in an apico-basal direction.

The excitatory process in both ventricles progresses toward the posterobasal region, which is activated latest in the cardiac cycle.

Repolarization. The pathway of the repolarization process cannot be investigated with the methods so successfully applied in the analysis of the depolarization process. Opening of the thorax changes the T waves. Because of the gradual character of the repolarization process the arrival of this process at the exploring terminals cannot be identified. We have tried to follow the pathway of the repolarization process, using the duration of the functional refractory period (F.R.P.) as a measure of the time necessary to restore cardiac excitability. At the end of the F.R.P. the myocardium resumes its ability to propagate an excitatory process. Since we could prove that at this particular moment the stimulating requirements are one and one-half times the diastolic level, the duration of the F.R.P. can be measured readily from strength interval curves.[13] The duration of the total refractory period, however, cannot be determined accurately. The duration of the F.R.P. shows slight differences in the successive layers of the ventricular wall: up to ±15 milliseconds. It can be seen (Fig. 4) that the end of the F.R.P. follows more or less closely the pathway of depolarization.

Intact human heart

The clinical cardiologist is mainly interested in the excitatory process of the normal and pathologic human heart. Even in this era of cardiac surgery, adequate analysis of the human heart is difficult, and mostly impossible. An extensive analysis of the human heart during operation takes such a long time that the safety of the patient may be jeopardized. Therefore, we used the Langendorff perfusion of the revived human heart.[1,2]

Reviving. We immersed 3 fetal hearts, each 7 months old, in a large container and

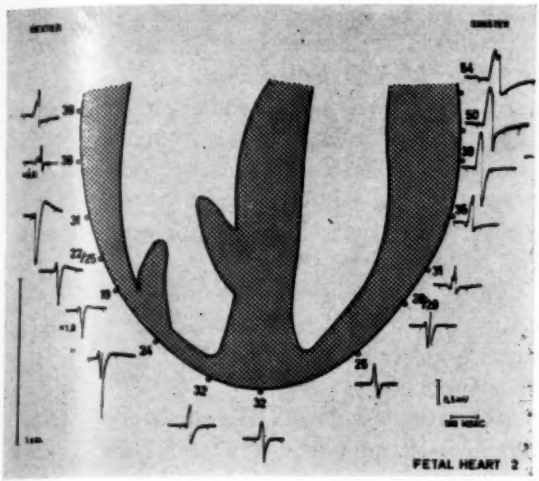

Fig. *5A*. Sagittal section of the ventricles just to the left of the ventricular septum. The numbers indicate the time of arrival, in msec., of the excitatory wave at the epicardial surface. Reference: beginning of ventricular depolarization.

used as reference electrode a large one situated at least 8 cm. from the heart. Therefore, the potential fluctuations of the reference electrode are very small in comparison with those of the exploring electrode, and the records may be called "unipolar." The perfusion fluid had no oncotic pressure, so that slight swelling of the heart, caused by interstitial edema, occurred. Boden's and our own experiments support the conclusion that the excitatory process of the heart in situ and that of the isolated heart are very similar. Records were made from 100 or more points in all hearts, and after the experiment these points could be identified on the epicardial surface of the heart.

Form of epicardial complexes.[14] There are no typical patterns for the left or right ventricle. Complexes of the rS type are found near the attachment of the anterior papillary muscle of the right ventricle, but also at the anterior surface of the left ventricle (Fig. 5).

Complexes of the qR type are present on the left ventricle, on two areas, e.g., the anterolateral portion of the left ventricle and the high posterobasal area near the left atrium. But qR complexes are also found on the right ventricle, on the left lateral and high anterolateral area and the posterobasal area. These complexes show initial negativity. We may conclude that the patterns which up to now have been considered typical for the right ventricle and left ventricle are also found on some portions of the heterolateral ventricle.

The form of the epicardial complexes at corresponding anatomic areas shows a striking correspondence. I may mention the opinion of Boden and Neukirch,[2] after their experiments on the isolated human heart, that the differences in the electrocardiograms of normal persons are probably caused mainly by extracardiac factors.

The posterior and lateral surfaces of the left ventricle show Q waves, as could be expected. But also the posterior surface of the right ventricle shows initial negativity. The area showing Q waves is located, therefore, at the posterior and lateral parts of both ventricles.

These Q waves all begin at the same time in the cardiac cycle and probably at the beginning of the left ventricular cavity potential. Their depth varies. The Q is deepest about one third of the way from apex to base. The deepest Q waves all are present on the posterior attachment of the ventricular septum and near the attachment of the posterior papillary muscles of the right and left ventricles (Fig. 6).

To demonstrate this relation in still another way, a section was made in the left ventricle, parallel with the ventricular septum and just to the left of it (Fig. 5*B*).

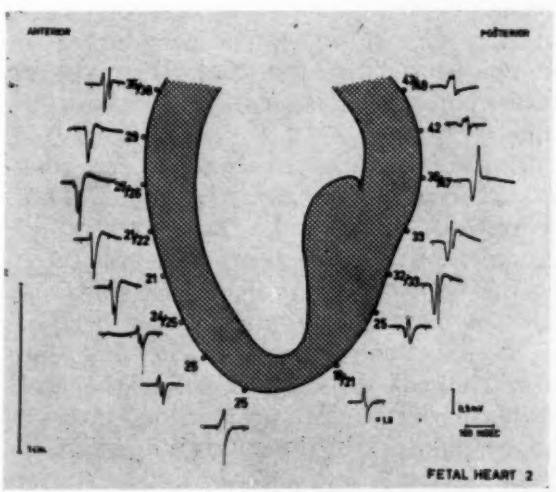

Fig. *5B*. Frontal section of the ventricles just to the left of the ventricular septum. The numbers indicate the time of arrival, in msec., of the excitatory wave at the epicardial surface. Reference: beginning of ventricular depolarization.

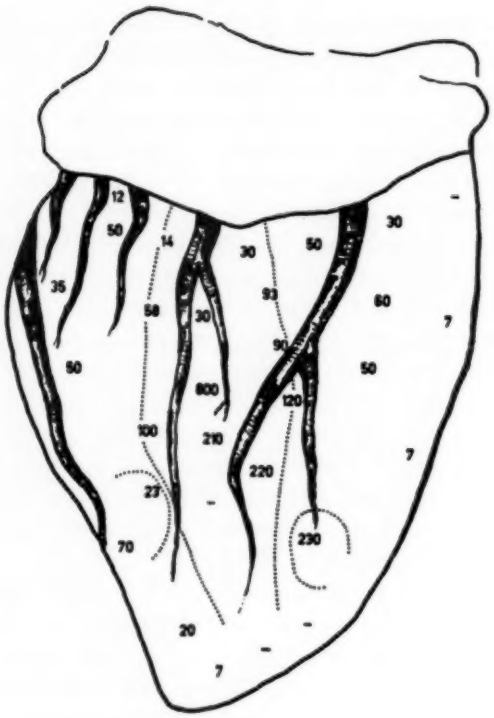

Fig. 6. Posterior view of the fetal heart. The numbers indicate the depth of the Q wave (in microvolts) in unipolar complexes from these places. Deepest Q waves are present one half of the way from apex to base, in the area overlying the posterior attachment of the ventricular septum. The attachment of posterior papillary muscles is indicated too.

The relation of the Q and the papillary muscle is evident. It is probable, therefore, that two factors, at least, contribute to the genesis of the Q wave: (1) excitatory wave in the ventricular septum progressing in an apico-basal direction, and (2) activation of the papillary muscles from their bases to apex.

Epicardial excitation pattern. The time of occurrence of the intrinsic deflection, if well developed, was measured in all records. All measurements were corrected to the beginning of the Q at the posterior surface. The times of arrival were grouped in 5-millisecond intervals. The first epicardial break-through occurs at the area trabecularis. At each 5-millisecond interval an enlargement of the epicardial area activated is seen. The anterior and posterior attachments of the ventricular septum appear to form no boundary for the epicardial excitation wave. Epicardial excitation occurs latest in the posterobasal region of both ventricles.

Elsewhere we described epicardial excitation as a double envelopment of the surfaces of both ventricles.[14]

Many years ago, Lewis[15] published a figure representing his considered view on excitation of the human heart. It is evident from Fig. 5*A* that there is a remarkable similarity between Lewis' considered view and our findings.

These conclusions are valid only for the 7-month-old fetal heart. We hope to repeat these experiments in the adult heart in the near future.

Let us now turn to abnormal excitation. Because of our clinical interest, we studied the changes occurring during acute coronary occlusion and in myocardial infarctions, 4 to 14 weeks old.

Acute coronary occlusion

Epicardial excitation pattern. In the ischemic area, all epicardial complexes show S-T elevations and abnormal Q waves. In contrast, epicardial excitation of the normal tissue surrounding the ischemic area remained constant up to 12 hours after the beginning of occlusion, i.e., up to the end of the experiment.

The epicardial surface of the ischemic area is activated late, up to 50 milliseconds, in the cardiac cycle. This delay is caused

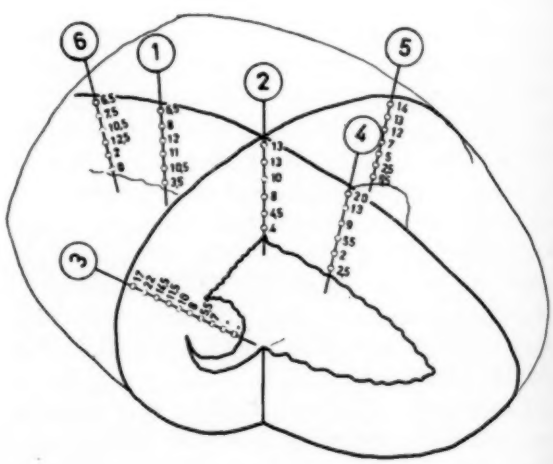

Fig. 7. Coronary occlusion during 2-3 hours. Spatial view of two cross sections of the left ventricle. The numbers at the epicardial surface indicate the needle electrodes. The smaller numbers at the intramural terminals indicate the degree of S-T shift measured (in mV.) immediately after ventricular depolarization. Needle electrodes *2*, *3*, *4*, and *5* have the highest degree of S-T shift in the subepicardial layer.

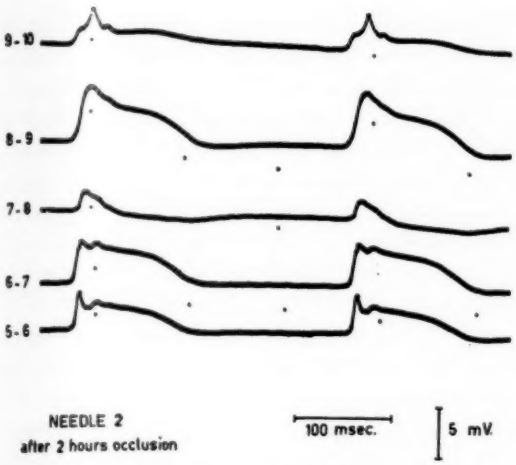

Fig. *8*. Intramural bipolar complexes 2 hours after beginning of coronary occlusion. The complexes show a large reduction in voltage and are notched. The S-T shift present points to the presence of a gradient of injury, making the outer layer positive in respect to the inner one.

by the decrease in conduction velocity of the excitatory process in the ischemic area.

The occurrence of premature beats during coronary occlusion is well known. In one case in which we followed the changes in electrical activity during coronary occlusion for 12 hours, premature beats occurred which showed a constant form of the epicardial and intramural complexes. They were presumably caused by activity of a constant focus. Because these premature beats remained present for a few hours, a complete epicardial excitation pattern could be recorded. The excitatory wave from this focus had the earliest epicardial break-through at a region which appeared to lie on the boundary of the infarcted area. Therefore, the focus was situated in the area of transition between the ischemic and normal myocardial tissue.

Intramural excitation pattern. In all instances, S-T-segment elevation was present in all unipolar leads from intramural terminals situated in the ischemic area, but the degree of S-T shift varied (Fig. 7). The S-T shift was measured at the end of ventricular depolarization in the ischemic area. At many places, maximal S-T shift was present in the subepicardial layers (needle electrodes 2, 3, 4, 5), and at other places in the mid-mural layers (needle electrode 6). A few hours later, S-T shift at needle electrode 2 was maximal in the subendocardial layers.

In the intramural layers of the ventricular wall surrounding the ischemic area, we could never reach a negative side of the boundary responsible for the S-T shift. S-T depression, however, was always found in the left ventricular cavity at the opposite side of the heart. We think that a sharply defined boundary is not present, but that there is a very gradual transition between injured and noninjured fibers.

Bipolar intramural complexes. During occlusion, the bipolar complexes registered between successive intramural terminals changed profoundly, but the observed changes did not follow a constant pattern.

The diameter of the coronary vessel occluded varied in different dogs, and the role of the collateral circulation responsible for the maintenance of a reduced blood supply could not be ascertained. It is not possible, therefore, to give an adequate description of the changes of the excitatory process as a function of the changes in blood supply.

The bipolar complexes may change in different ways. In some cases, only broadening of the bipolar complex was found. In

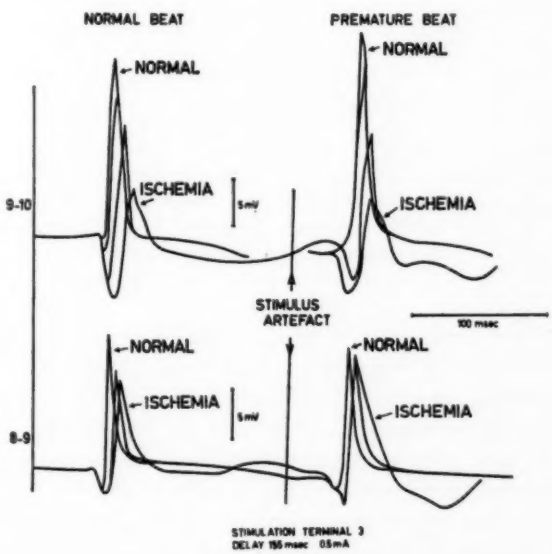

Fig. *9*. Bipolar complexes 8-9 and 9-10. The complexes labeled *ischemia* were recorded 5 minutes after beginning of coronary occlusion. A negative deflection precedes a small and broad positive deflection, falling late in the cardiac cycle. They retain their form during endocardial stimulation. The complexes labeled *normal* were recorded 22 seconds after release of coronary occlusion. The transition of the abnormal complexes to normal, intramural complexes can be clearly seen.

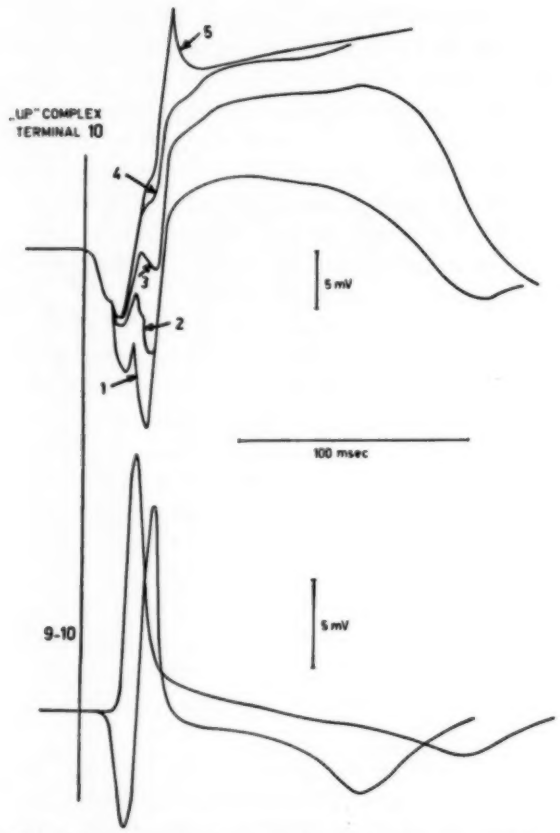

Fig. *10*. Changes in complexes during progressive coronary ischemia. Complex *1* was recorded 15 seconds after beginning of coronary occlusion; complex *2*, 60 seconds; complex *3*, 100 seconds; complex *4*, 120 seconds; complex *5*, 225 seconds after beginning of coronary occlusion. The arrows indicate the location of the intrinsic deflection. Bipolar complex 1 was registered synchronously with unipolar complex 1, complex 2 synchronously with unipolar complex 5. The downstroke of the "R" in unipolar complex 5 occurs synchronously with the downstroke in 9-10, and is caused by excitation of muscle layers in contact with terminal 10.

other cases, there was a loss of voltage in the bipolar complexes, but this change was always associated with broadening of the bipolar complexes. Fig. 8 is a typical illustration. The complexes are broad and show loss of voltage, notching, and S-T shift. The broadening of these complexes is caused by a diminished conduction velocity of the excitatory process in the ischemic area—sometimes 10 cm. per second or less. The loss of voltage can possibly be related to a reduction of the membrane action potential. The notching may be caused by the fact that the muscle fibers in the ischemic area are not changed to a similar degree by anoxia, and do not conduct the excitatory process at the same rate.

Sometimes, and most frequently after the occlusion of a major branch or after prolonged occlusion of the coronary vessel, complexes of a perplexing form are found (Fig. 9, complex labeled *ischemia*). These bipolar complexes show a large reduction in voltage of the R, and a large negative wave precedes the "R." Sometimes this R wave may disappear and the complex is completely negative.

Bipolar complexes of this type may even be present in successive layers of the ventricular wall. The changes which occur after restoration of blood supply may shed some light on the genesis of these complexes (Fig. 9). It can be seen that the depth and duration of the negative wave diminish. Simultaneously the positive deflection increases in voltage and also falls progressively earlier in the cardiac cycle. After 20 to 30 seconds it is very high again and only a small negative wave precedes the positive deflection: the complex has regained its preocclusion form. It is an astonishing fact that the disappearance of the ischemic complexes occurs very rapidly, mostly within one-half to one minute, after the coronary circulation has been re-established. During that period, multiple ventricular premature beats frequently occur. Many experiments terminated in ventricular fibrillation during that period.

It is possible that these bipolar complexes are caused by an increase in distance between sources and sinks of the polarized surface which represents the electrical effects of excitation.

Changes in unipolar epicardial and intramural complexes. During acute occlusion the form of the QRS complex, of the unipolar epicardial complexes, [6,16,17] and, as we could prove, also of the intramural complexes, changes in the following manner: (1) decrease in voltage of S, sometimes even disappearance of the S; (2) a gradual delay in the onset of the intrinsic deflection; (3) decrease of the voltage and duration of the intrinsic deflection; and (4) perhaps complete disappearance of the intrinsic deflection.

Fig. 10 depicts the changes in the form of the unipolar intramural complex during coronary occlusion. The intrinsic deflection demonstrates the changes just described.

In the complex 4 the intrinsic deflection has disappeared; only a small notch is present on the ascending limb of the monophasically deformed complex. One might be led to conclude that the excitation wave does not reach this terminal anymore.

However, because the bipolar complex 9-10 shows a downstroke caused by excitation of 10, this conclusion is wrong. Therefore the disappearance of the intrinsic deflection does not necessarily mean that no excitation of the ventricular muscle in contact with the exploring terminal occurs. With prolonged ischemia the upstroke increases and upright deflection of short duration appears (complex 5, Fig. 10), followed by a slow downstroke coinciding with the last portion of the descending limb of the bipolar complex 9-10. This deflection in the unipolar complex, therefore, is caused by local excitation at terminal 10.

Chronic myocardial infarction

In 1934, an important paper by Wilson, Johnston and Hill[18] was published which forms the basis of much of our knowledge about the electrocardiographic changes in myocardial infarction.

Since the excitatory process spreads from the endocardial surface to the outer layers, it is difficult to see how it can reach the outer layers when the inner layers are dead or replaced by scar tissue. The aforementioned authors were unable to understand how the excitatory process can cross the infarcted tissue unless they supposed that this tissue is penetrated by living Purkinje fibers or by surviving strands of ordinary muscle.

With the methods outlined at the beginning of this lecture, this important problem was tackled. Epicardial and intramural excitation patterns were investigated.

Epicardial excitation. The epicardial excitation pattern in myocardial infarction was changed profoundly. The unipolar complexes showed definite abnormalities, even if the infarction was situated in the subendocardial layers. Up until now we have not encountered a situation in which an infarction of the subendocardial region did not result in an abnormal epicardial complex. The major change in the QRS complex was the occurrence of abnormal

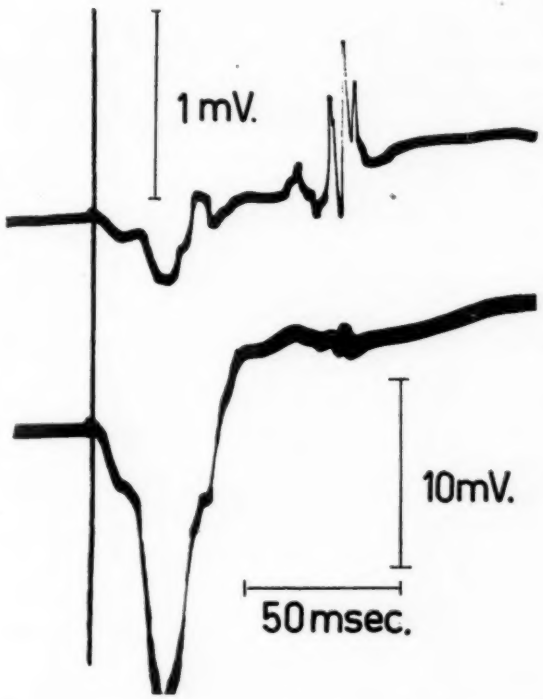

Fig. *11.* Differential complex (*upper record*) synchronous with unipolar complex (*lower record*) from one of the terminals of the differential electrode placed on the epicardial surface of a transmural infarction. The small deflections which occur 75 milliseconds after the beginning of QRS are caused by excitation of tissue in contact with the differential electrode.

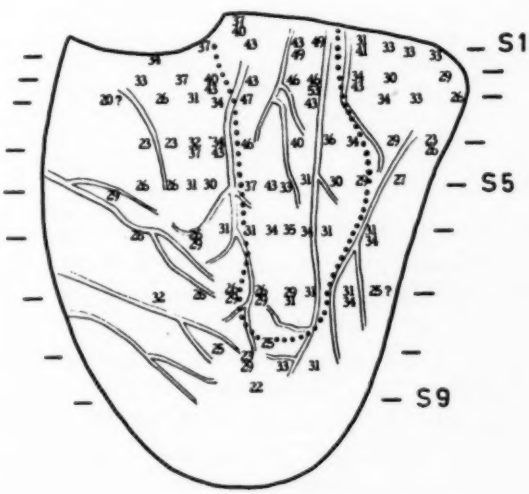

Fig. *12.* Activation time (msec.) of epicardial surface in myocardial infarction. The epicardial surface above the subendocardial infarction, indicated by the dotted line, is activated late in the cardiac cycle. In the region bordering the A-V groove an area is activated with only slight delay (*30*, 41 msec.) and is lying close to an area activated much later (*49*, 53 msec.). Between those two areas, fibrous tissue strands reach the epicardial surface, acting as a boundary for the crossing of the excitatory wave.

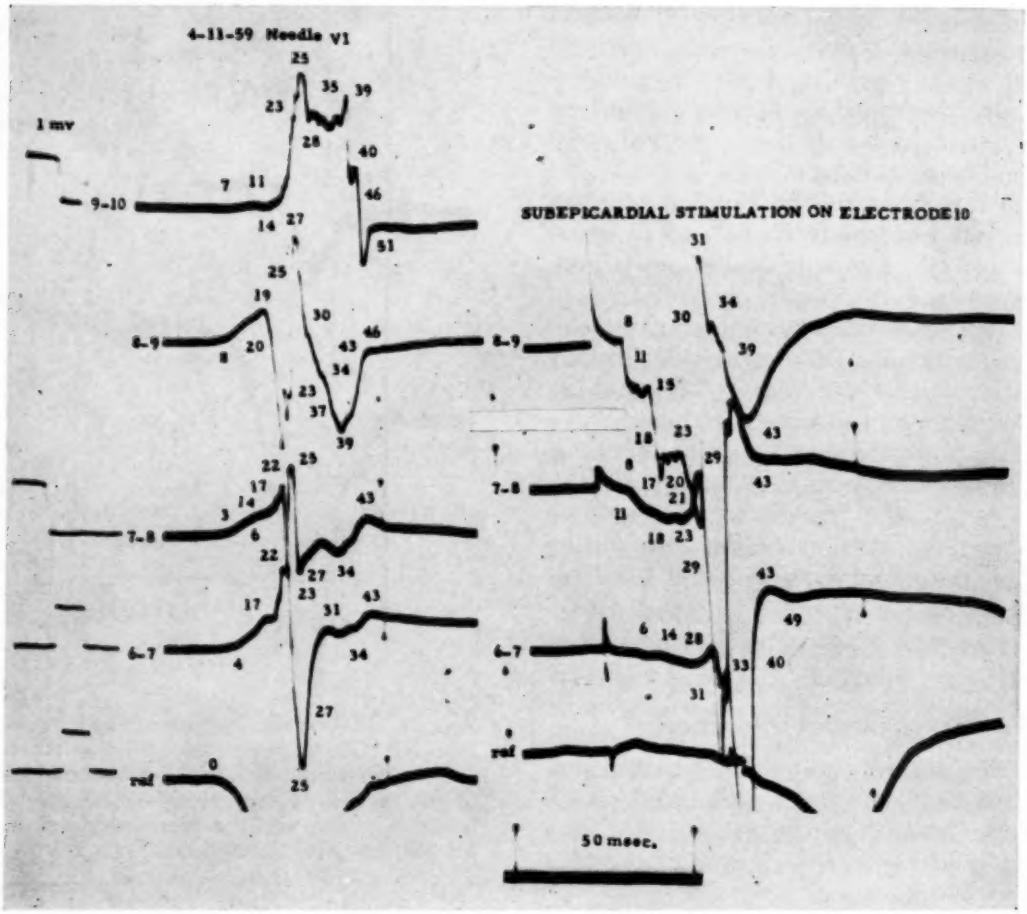

Fig. *13.* Bipolar complexes from terminals lying in the infarcted area. The voltage of the complexes is greatly reduced, multiple notches are present, and the complexes are very broad. The numbers indicate the time of occurrence of the notches and deflections after beginning of left ventricular cavitary potential. Many small excitation waves are present in this area. During subepicardial stimulation the polarity of the bipolar complexes reverses, and the complexes are grossly deformed and notched.

Q waves. Under the conditions of our experiments the normal Q wave was never deeper than 2.2 mV., and the duration from beginning to nadir did not exceed 8 milliseconds. The total duration of the Q never exceeded 12 milliseconds.

In all of the hearts with chronic myocardial infarction it appeared that the area which showed abnormal Q waves coincided rather closely with the infarcted area. The anatomic infarction, as detected by very careful microscopic examination, was only slightly smaller than the area showing changes in electrical activity.

In all cases of subendocardial infarction the beginning of the epicardial Q was synchronous with the beginning of negativity of the left ventricular cavity, suggesting the correctness of Wilson's "window theory."

The intrinsic deflection in the unipolar complexes of the area overlying the infarction was changed and sometimes difficult to recognize. In Fig. 11 the unipolar complex recorded from the epicardial surface of a nearly complete transmural infarction is shown. In the complex, small pips which occur from 75 to 80 milliseconds after the beginning of the QRS complex are seen. The duration of the main QRS complex is 50 milliseconds.

A differential electrode was placed on that area (Fig. 11). The arrival of the excitatory wave at the muscle fibers in contact with this differential electrode is signaled by the occurrence of small, fast

deflections. Therefore, the deflections in the unipolar complex are caused by local excitation of the subepicardial muscle layers. This excitation occurs late in the cardiac cycle (75 to 80 milliseconds), at the moment at which depolarization of the remainder of the heart is completed and even repolarization in a large part of the ventricles is taking place. The pathway of excitation in this area of a few square millimeters is very bizarre, but, nevertheless, the pathway is constant from beat to beat. No variations, however small, are allowed: the pathway of excitation is strictly determined.

The form of the differential complexes shows that, even in that small area, large desynchronization of excitation occurs; the excitatory wave is highly fragmented.

Time relations of the epicardial surface. Analysis of the time relations of epicardial break-through above a subendocardial infarction reveals some interesting facts. In most of the cases it occurs late in the cardiac cycle (Fig. 12).

An accurate analysis of epicardial excitation reveals that areas lying very close together may show great differences in times of arrival of the excitatory wave. In this case an offshoot of fibrous tissue from the subendocardial infarction reached the epicardial surface and acted as a barrier for the crossing of the excitatory process from the region activated early toward the neighboring region activated late in the cardiac cycle.

Bipolar intramural complexes (Fig. 13). The form of the bipolar complexes in the intramural leads was changed: (1) The voltage was reduced; sometimes a large reduction of voltage was present. (2) The complexes showed broadening and multiple notching.

They may become polyphasic. Small, fast deflections are nearly always present. In our opinion, these small deflections are caused by successive excitation of strands of muscle fibers in contact with the exploring terminals. During subepicardial stimulation the polarity of the bipolar complexes points to the presence of a highly fragmented excitatory wave, progressing in an endocardial direction.

Intramural time relations. A gradual "mopping up" process of the intrainfarction muscle fibers takes place. It takes a long time before all of the intrainfarction muscle fibers are depolarized. The excitatory waves take devious routes, but they are constant from beat to beat.

Wilson, in the paper already cited, wrote that it was the hope of himself and his colleagues that studies of the refractory period in the infarcted region would yield important information in regard to the ability of the affected muscle to respond to the excitatory process.

We measured the excitability of intrainfarction muscle fibers (Fig. 14). There appeared to be no large change for cathodal and anodal excitability, compared to normal ventricular muscles. Sometimes the diastolic threshold was somewhat higher than in normal muscle, perhaps due to short-circuiting by nonexcitable tissue.

How does the excitatory wave reach the muscle fibers in the infarcted area? We looked for evidence of Purkinje activity in the subendocardial tissue, but could only demonstrate it in a few cases. In most of these cases, Purkinje activation occurred at a normal time, at the beginning of the left ventricular cavitary potential. No delay in activation of the subendocardial Purkinje fibers could be demonstrated. In

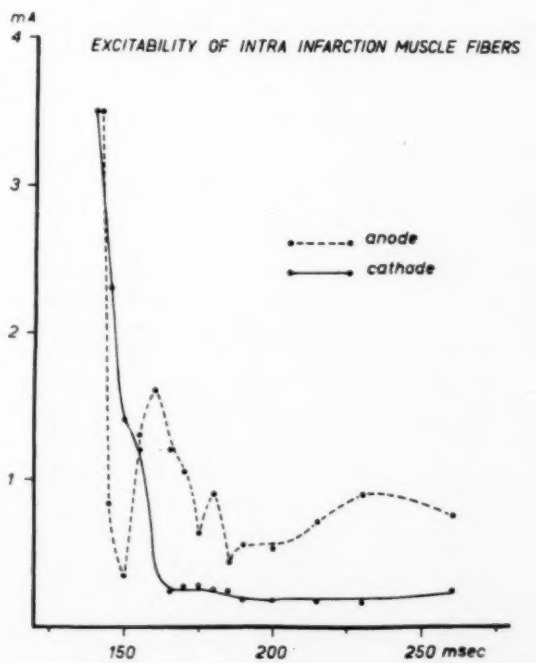

Fig. *14.* Excitability of viable muscle fibers lying in a 6-week-old infarction. The excitability of the surviving muscle fibers is nearly normal.

only one case were subendocardial Purkinje fibers activated relatively late in the cardiac cycle.

Because of the tangential excitation which may take place in the outer layers above the infarcted area, the Q/R relation does not necessarily give evidence about the degree of intramural extension of a subendocardial infarction.

The Q in subendocardial myocardial infarction is caused mainly by the reduction in voltage generated during activation of these regions. In only one case could we find evidence of a delay in transmission of the excitatory process from the Purkinje fibers to the muscle fibers.

Closing remarks

Mr. Chairman, looking back to what has been achieved with the methods given to the world by the man whose birthday we commemorate today, we are deeply impressed by the great amount of work that has been done. But looking forward, we feel humble because there is still so much to do. One point is very important. The bridge separating electrocardiography as a part of physiology from electrocardiography as a part of clinical medicine has been bridged by workers in both fields: physiologists working in one direction, clinicians, in the other one. They can at ast understand what the other party is doing, because more or less they have learned to speak a common language.

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Discussion

W. TRAUTWEIN,* Heidelberg, Germany. Before the beginning of the general discussion I shall try to add some information which concerns automaticity and the effects of vagal and sympathetic stimulation on heart muscle fibers. At first, I should like to mention the differences in the cyclic membrane potential changes between fibers spontaneously active and those which do not beat spontaneously. Whereas in the ventricular and atrial fibers which are excited by conduction the diastolic membrane potential remains constant, the fibers of the sinus and Purkinje system show a spontaneous slow depolarization to threshold in diastole (see Fig. 1). Within the sinus the rate of this slow diastolic depolarization is greatest at the locus of the pacemaker. A few millimeters apart from it the fiber is excited by conduction. The analysis of the mechanism underlying spontaneity is not yet complete, but it may be said that there is evidence of a higher resting sodium permeability in spontaneously beating fibers than in the nonspontaneously beating ones.

Fig. 1,*B* shows the effects of vagal stimulation on the membrane potential of a spontaneously beating frog sinus fiber, presumably taken at the pacemaker. Again, there is a slow diastolic depolarization, which progresses smoothly into the steep rise of the action potential. The peaks of the action potentials are cut off and cannot be seen on the record. The vagus was stimulated at a rate of 10 shocks per second during the interruption of the reference line. The pacemaker potential is immediately suppressed and the maximal diastolic potential increases. The upper tracing (Fig. 1,*A*) shows the effects of acetylcholine on the membrane potential of a spontaneously beating dog sinus fiber. The arrow indicates the application of acetylcholine, which immediately causes a suppression of the pacemaker potential. After two beats, which arise in the deeper part of the preparation and are conducted to the impaled superficial fiber, the preparation is arrested. The two main features of the inhibition shown in this figure are the arrest of the heartbeat and the hyperpolarization. The well-known shortening of the duration of the action potential can also be seen.

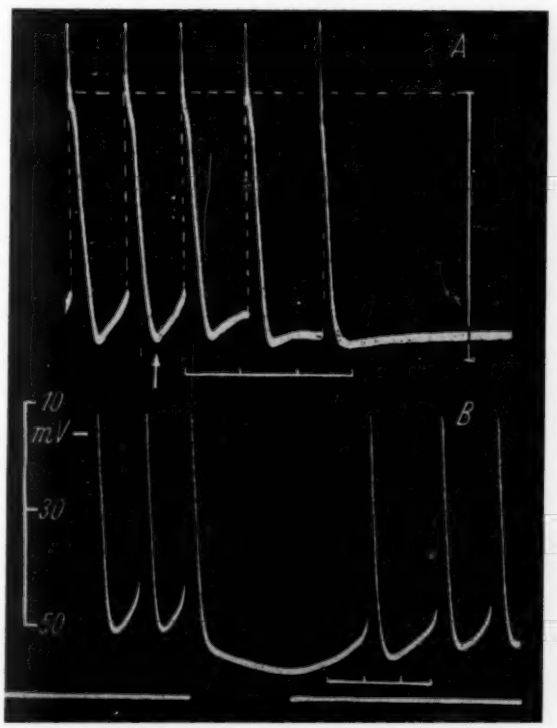

Fig. *1*. *A*, Spontaneously beating dog sinus fiber. The arrow indicates application of acetylcholine. Note the suppression of the pacemaker potential and the slight hyperpolarization. The third to fifth action potentials are conducted responses. Ordinate, 80 mV.; abscissa, second (from Trautwein: Physiologie der Herzirregularitäten. *In* Spang: Die unregelmässige Herztätigkeit, Stuttgart, 1957). *B*, Spontaneously beating frog sinus fiber. The vagus was stimulated at a rate of 20 per second during interruption of the reference line. Abscissa, second (from Hutter and Trautwein: J. Gen. Physiol. 39:715, 1956).

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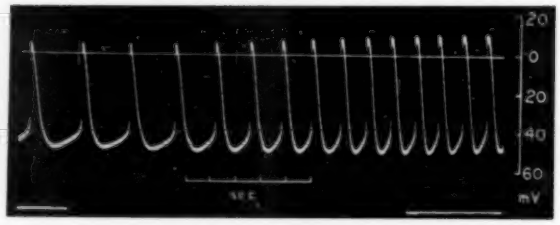

Fig. 2. Effect of sympathetic stimulation on the slope of the pacemaker potential and the amplitude of the action potential. Stimulation of the vago-sympathetic trunk (atropinized preparation) at a rate of 20 per second during the interruption of the reference line. (from Hutter and Trautwein: J. Gen. Physiol. 39:715, 1956).

The mechanism of vagal inhibition has been extensively studied, both by electrophysiologic and radioisotope techniques. The experimental evidence fits perfectly well into the concept of ionic theory of excitation in heart muscle which Dr. Weidmann presented. It supports the view that acetylcholine acts by specifically increasing the membrane conductance for potassium. Such a mode of action explains the phenomenon which I have just described. For instance, the hyperpolarization and suppression of the pacemaker potential are the result of the rapid increase in potassium permeability, by which the membrane potential is driven toward the potassium equilibrium potential, thus stabilizing the membrane at a high membrane potential. Moreover, the shortening of the action potential by acetylcholine or by vagal stimulation is due to the specific increase in potassium permeability increases the efficiency of the driving force during the plateau. Thus, the normal repolarization is accelerated by an additional increase in the permeability to the repolarizing ion.

Although the inhibitory effect of acetylcholine is quite well understood as an increase in the passive potassium permeability, an explanation of the effect of the sympathetic stimulation or adrenaline is more difficult. Fig. 2 shows the effect of the sympathetic stimulation on an innervated excised sinus venosus of the frog heart. During the interruption of the reference line the sympathetic trunk was stimulated. This caused the rate of the slow depolarization to increase progressively, thus increasing the frequency of the sinus, while the threshold remained nearly constant. At the same time the overshoot and the rate of rise increased. A slight rise in membrane potential clearly accounts for this latter effect on corresponding mammalian tissue. The loss of plateau in a hypodynamic or metabolically inhibited fiber is mostly counteracted by adrenaline, and the duration of the action potential may be prolonged to control values. All evidence we have favors the assumption that adrenaline does not act by changing passive permeabilities of the fiber membrane, but rather by increasing the activity of a metabolically driven ion pump. This brings us back to Dr. Weidmann's analysis of the events during the plateau. I should like to open the general discussion with the question: Should we assume that active ion transport affects the time course of the action potential exclusively by controlling the extracellular potassium and/or intracellular sodium concentration, or is it perhaps possible that the pump moves a net charge, which produces a change in membrane potential?

S. WEIDMANN, Bern, Switzerland. In my opinion there is no conclusive evidence to show that active transport contributes to the time course of the action potential, in the sense that the rate of pumping for certain ions changes in the course of one cardiac cycle. One might put forward the hypothesis that a net inflow of potassium ions during the plateau phase is responsible for the long-lasting action potential which is typical for cardiac tissue. The shortening of the action potential observed with metabolic poisons would then find an easy explanation. Also it had been suggested that repolarization might be due to active transport of sodium ions from inside out. But, again, I should like to stress that there is not enough evidence to place too much weight on such a hypothesis.

Heart-vector and leads

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The investigation of the electrical action of the heart without serious intervention in the life processes must in practice be based on measurements of potential on the body surface. The development of research has followed two entirely different paths. The first one is the collection of empirical data concerning the relation between heart disease and the electrocardiograms taken from the periphery, and is the method of conventional electrocardiography, the importance of which I need not emphasize. Neither do I need to stress the great merit of Einthoven in this connection. But Einthoven led the way to another approach to this problem in originating the notion of what is now called the heart-vector. He drew attention to an interpretation of the ECG as a consequence of a series of events beginning with an electrical action inside the heart muscle. This electrical action sets up a field of current in the trunk, and this in its turn generates a distribution of potential over the body surface (Fig. 1). This connection of inside action and outside effect represents a physical problem and this may explain why a physicist has the honor of speaking to you on this occasion.

It is noteworthy that Einthoven tackled the subject geometrically. His triangle (Fig. 2) is too well known to make it necessary to explain it here in detail. But it is worth while to remark that this method is not only geometrical but also intuitive, and naturally so. The physical laws governing the field of current in a three-dimensional conductor, such as the human trunk, have an analytical form; they are formulas. And although they are partly expressed in the symbols of differential geometry, the only possibility of drawing conclusions from them in a rational way is to solve a partial differential equation with boundary conditions.

It must be said that the work of so many investigators after Einthoven has created a difficult situation. Each of them has given his own idea concerning the relation between heart-vector and leads, and almost all of these systems are both geometrical and intuitive, and, therefore, irrational. I shall not mention names but it is my conviction that this variety of systems of vectorcardiography has hampered the development of vectorcardiography, and that not only, and not even mainly, because they are not exact or not correct. They give results that are appreciably different, and, therefore, one investigator cannot interpret the results, the patterns, obtained according to the method of another. Standardization is urgently needed, and I think in this respect everybody agrees, provided that the system he uses should be accepted as a standard. To my mind, there is only one way out of the present chaos, and that is a rigorous study of the inside-outside relation already mentioned. It goes without saying that physics has to

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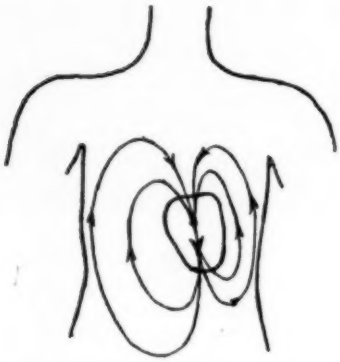

Fig. *1*. Field of current in the human trunk, caused by the electrical action of the heart.

contribute to this program, and that the basis of the theoretical treatment must be analytical.

Several properties of the object of study, the human heart located inside the trunk, have to be considered. These are properties of the heart and of the trunk both. The principal ones are the following: (a) the nature of the electrical sources in the heart muscle; (b) the distribution of these sources over the heart; (c) the shape of the boundaries, in the first place, of the thorax, and the position of the heart relative to it; (d) the electrical properties of the conducting tissues, especially those outside the heart. Heterogeneity and also anisotropy should be taken into consideration.

The first point, a, was discussed by Dr. Weidmann and Dr. Durrer this morning, and I may use their conclusions. The sources are essentially of dipole character, and each elementary source, generated by one muscle fiber, is so small that we need not consider their dimensions and distances in our macroscopic treatment.

Concerning all further points, b, c, d, the solution of the problem, the relation of heart-vector and leads, as given by Einthoven, is a simplified assumption. (b) The dipole is a point-shaped source and located in a fixed point. (c) The thorax is spherical and the source is in its center. Only the phenomena in the frontal plane are discussed. (d) The material in the trunk is homogeneous and isotropic.

As a first approximation this conception is certainly valuable and has been useful in many clinical discussions. But some of Einthoven's followers have seen in it an exact description of the true events, and this is much more than Einthoven ever pretended.

The view of the physicist is different from that of the physician or physiologist, as I mentioned before. May I outline the main ideas developed in the last fifteen years or so. I hope you will not object too much when, in doing so, I give you a more or less one-sided view.

Returning to the points a, b, c, d, it may be stated that b is the most essential one in a certain aspect. So we need not assume that c and d hold. If only the dipole is point-shaped and stationary, the trunk may be built in any way in regard to its shape, the position of the heart, and the material. In this case, all equations relating dipole and leads are linear, i.e., they contain only sums (or differences) of the variables. Then, leaving undecided and undiscussed all that is in between dipole (or heart-vector) and lead, we must conclude that every lead has a linear relation to the dipole. As we must and shall use an analytical description, this dipole must be defined and handled as a set of components, most easily in an orthogonal coordinate system. Let the orthogonal components of the heart-vector be X, Y, Z, and V be an arbitrary lead; then the linearity just mentioned has as a consequence a linear relation between V, on the one side, and X, Y, Z, on the other, so:

$$V = aX + bY + cZ \qquad (1)$$

In this formula, X, Y, Z are functions of time; they vary during the heart beat and are repeated almost periodically. The

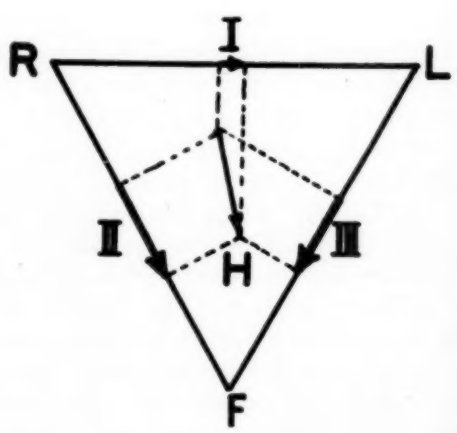

Fig. *2*. Heart-vector projected on the sides of the Einthoven triangle.

coefficients *abc*, on the other hand, are constant, i.e., independent of time. It is by this equation that we express the linear relation of inside "cause," *XYZ*, and outside "result," *V*.

I shall remind you very briefly of how we can make practical use of this equation as the basis of a lead system of VCG. From three equations of the type of the equation mentioned, the three unknowns can be solved by elementary algebra. To find the solution numerically the 3×3 coefficients must be known. They can be determined by model experiments, and it is here that points c and d of our list of conditions come in. The shape of the body does not give serious difficulties and has seldom been the subject of discussion. But d is a more important point. Anisotropy has been neglected by all, but I have reasons to doubt the justifiability of this neglect. The opinion about heterogeneity seems to depend on nationality. Whereas in this country we have reckoned with an appreciable heterogeneity, the investigators in the United States have worked with a homogeneous model. I suppose that the reality is intermediary, and I hope that they believe so too.

The numerical solution of the three equations gives the orthogonal components *XYZ* of the heart-vector as a linear function of three independent leads. By electronic means a display can be realized giving the heart-vector and the vectorcardiogram in any projection. These technical details do not belong to the subjects of this day.

So far this analytical procedure does not need any geometrical means. But if desired, these can be deduced from our equation. The latter can be interpreted as a relation between the scalar quantity *V*, a voltage, and two vectors, the heart-vector with orthogonal components *XYZ* and the so-called lead-vector with components *a, b, c*. *V* is the so-called scalar product of the two vectors *XYZ* and *abc*. It is equal to the product of the magnitude of one of them and the projection of the other on this one. This interpretation is secondary but popular among physicians. It can be generalized by the conception of the image space in which every point of the body surface has its image.

But let us leave this imaginary world to return to reality. How can we check whether the assumptions with respect to b, c, and d are correct, i.e., near enough to the truth to be the foundation of a clinical method? Of these assumptions, b, the dipole hypothesis, is certainly the most essential one. Is it a good approximation to assume that the dipole action is confined to a region the dimensions of which are small with respect to the corresponding dimensions of the thorax? There are two ways to answer this question.

1. The first one in its most simple and at the same time most general form is a method indicated by the late Dr. Becking. It can be derived from the linear equation (1). From three equations of this type, giving the voltage in three leads, each expressed in the time-functions *XYZ*, the latter ones can be solved and expressed as linear functions of the three *V*'s, which are also time-functions (electrocardiograms). Now these three linear functions of three *V*'s can be substituted in a fourth equation of the same type, valid for a fourth independent *V*. In this way this fourth lead is expressed linearly in three other leads. This must be true for any body independent of the position of the dipole, if only it is point-shaped (or at least very small) and stationary. It is easy to test such a linear relation of four leads by electronic means, but I will not explain to you here how it is done. The result is that there are deviations from the ideal case great enough to be of practical importance. It must be emphasized that these are measurements on human bodies. They have nothing to do with model experiments or assumed coefficients. They show in the most direct way that the dipole hypothesis, although it has some meaning, is a too fargoing simplification.

Older than the Becking method but intimately related to it is the test of the dipole hypothesis that is known as the mirror-image method or the cancellation method. It is so well known that I shall not explain it here. As to the result, the opinions are not entirely unanimous. Some investigators have stated their belief that according to this method it can be proved that the dipole is point-shaped and stationary. But I cannot help supposing that in

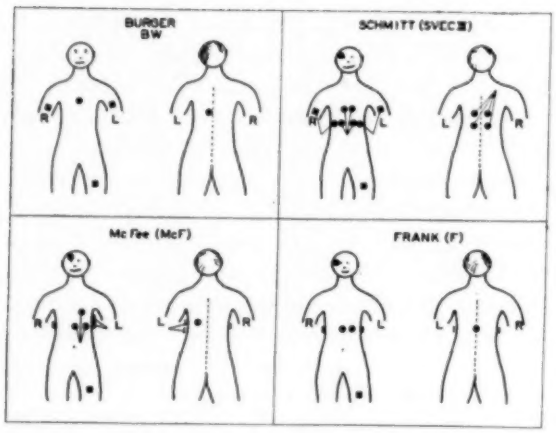

Fig. 3. Situation of the electrodes in the lead systems of Frank (F), Schmitt (S), McFee (M), and Burger (B).

some cases this is wishful thinking. In many cases, according to my own experience and that of others, the deviation from the pure dipole action is too great to be neglected. This is the more urgent since it is emphasized that a good cancellation may be arrived at with dipoles distributed over a volume that is not at all small with respect to the thorax.

2. A quite different test of the dipole hypothesis is a practical one, the comparison of loops obtained by different lead systems of VCG. By looking at the loops a subjective judgment of the correspondence is obtained, which has all the drawbacks of subjectivity, but at the same time all the advantages. But yet the comparison of loops obtained by different lead systems must be expressed in a quantitative way. Therefore, we have awarded marks to the agreement, calling 10 the best agreement that can be expected, such as is shown by successive heartbeats in one and the same system. The correspondence of loops which show no relation at all is called zero. An advantage of these scores is that we can weigh the criteria according to their clinical significance, such as left or right preponderance and clockwise or counterclockwise rotation.

Long ago, when applying this method in comparing two systems of our own and a system without physical foundation, we found that the correspondence of those two was better than that of each of them with the third. But even when two systems based on model measurements are compared, the agreement in some cases is sometimes far from ideal. This cannot be ascribed to wrong coefficients alone. If this were so, the noncorrespondence should be of a simple kind, to be expressed by a linear transformation. This relation I hope to explain later. For the moment it may suffice to say that several investigators agree in the explanation of insufficient agreement in the majority of cases: the heart is not acting as a point-shaped dipole but as a distribution of dipoles over the heart muscle. Since the latter is not small with respect to the dimensions of the trunk, the approximation of the dipole hypothesis is insufficient, especially for the sagittal component, i.e., the component in the direction of the smallest dimension of the human thorax.

Several investigators, and these are all physicists, have tried to take this circumstance into account. This problem could only be solved by applying an infinitely great number of electrodes, as was proved by Gabor and Nelson. But for practical reasons the number has to be restricted, and these are the arguments that count heavily for every physician applying vectorcardiography.

The correct way to investigate the influence of the dipole distribution over the heart, i.e., in a part of the thorax that is not at all small, is to use a model and move the artificial dipole in it. By experiments of this kind it is possible to study the effect of dipole position. Then an attempt can be made to design a system, the leads of which will not depend too much on the dipole position, so that they can be used to find the total dipole, irrespective of the distribution of its local constituents. This was carried out by some American investigators in a very elegant way. In our system we did it less sophisticatedly.

The old method of comparison, the award of scores, was the first one we applied to get an idea of the effectiveness of the use of more than the essential minimum number of electrodes, namely, four.

Lately, we have been comparing four systems, all with a sound physical foundation and corrected for dipole location. Three of them, all of American origin, are based on a homogeneous model. They are the systems of Frank, Schmitt (SVEC

III), and McFee. The McFee system was communicated to us by the author, but has not yet been published as far as I know. The positions of the electrodes in the four systems are indicated in Fig. 3. The weights attached to the contributions of each electrode are effected by resistances as described in the publications of Frank and Schmitt. In McFee's system the two electrodes at the left side have the same weight, just as is the case with the three precordial electrodes.

The fourth system is one of our own, in which the quantitative relations were deduced from a heterogeneous model in which the specific resistance of the air-filled lungs is taken to be four times that of average human tissue.

The number of electrodes of the systems compares as follows: homogeneous model—F, 7 electrodes, S, 14 electrodes, M, 9 electrodes; heterogeneous model—B, 5 electrodes.

This number is important for the decision of which system to use clinically, just as is the electrode location, especially that of the dorsal electrode or electrodes.

The result of the comparison is shown in Fig. 4. It has been deduced from some 150 to 200 comparisons, mainly cases of heart disease. The score is given for the agreement of the frontal and of the horizontal projections, respectively. All combinations of the four systems figure in this diagram. The following conclusions can be drawn from it.

1. The agreement is better for the frontal than for the horizontal projection. This is a consequence of the uncertainty in the sagittal component of the heart-vector, caused by the small dimension of the human trunk in sagittal direction.

2. The agreement of the "American" lead systems F, S, and M *inter se* is better than that of B with each of these three. This may be caused by two circumstances, the small number of electrodes in B (5) that makes it more difficult to reduce the influence of dipole location, and the assumption of heterogeneity of the thorax in the B system.

3. The agreement between the S and M systems is so satisfactory that for practical purposes one of the two can be omitted. Since S has more electrodes than M, which is a complication in clinical use, we think that system S can be abandoned and M chosen in its place.

Only in a fraction of all cases does real discrepancy exist between any two systems, i.e., a difference so pronounced that it would lead to a different diagnosis. Anyhow, this fraction, of the order of 20 per cent for the worst combination of lead systems, is too great to be accepted.

In the last few months we have applied quite a different method of comparing lead systems. This procedure was tried tentatively some years ago, but now we have used it more rigorously. We arrived at it by the following line of thought. If indeed the dipole hypothesis were true, then two arbitrary lead systems, each of them with any number of electrodes, should have a simple relation. From our fundamental equation

$$V = aX + bY + cZ,$$

it can be deduced that each coordinate of a point of a loop in one of two arbitrary lead systems is a linear function of the coordinates in the other system. This is true whatever be the values of the coefficients chosen for the two systems; they may be correct or entirely wrong. The mathematical relation between two such lead systems (let us call them C and D) can be expressed by the following set of formulas:

$$\left.\begin{aligned} X_D &= p_1X_c + q_1Y_c + r_1Z_c \\ Y_D &= p_2X_c + q_2Y_c + r_2Z_c \\ Z_D &= p_3X_c + q_3Y_c + r_3Z_c \end{aligned}\right\} \qquad (2)$$

I regret that I cannot describe this relation

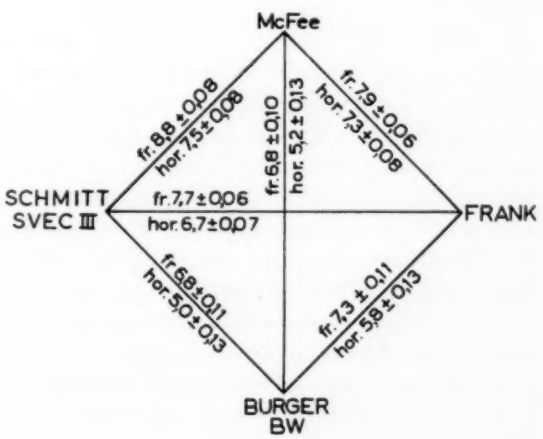

Fig. 4. Marks awarded to the agreement of vectorcardiograms. Averages and standard errors.

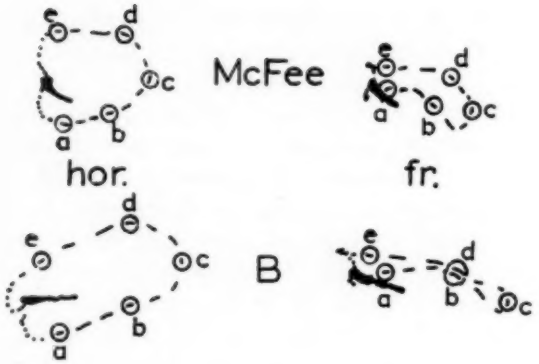

Fig. 5. Five synchronous points, *a*, *b*, *c*, *d*, *e*, on frontal and horizontal projections of the vectorcardiogram in two lead systems.

adequately without algebra, but here again we have an example of the fact mentioned before that the algebraic form is primary. Yet it is possible to mention examples of linear relations or transformations that are expressed by a special form of this set of three linear equations and may be interpreted geometrically in a simple way. I refer to a rotation and a one-sided or all-sided dilatation or compression. Another transformation of this kind, less known in daily life, but important in our problem is a so-called shear. In a special case it can be described geometrically as a horizontal displacement of all points to an extent proportional to the vertical coordinate. It is precisely this transformation that plays an important part when VCG systems are compared. This was evident from clinical discussions before it was demonstrated exactly by mathematical treatment.

I have hesitated a good deal before deciding to say more than a single word about this more exact mathematical treatment. I determined to do so because I prefer to be considered by you as a bore rather than as a mathematical witch doctor.

We can be certain a priori that the set of equations (2) does not hold generally because the dipole hypothesis is not generally true. So we have to reckon with the fact that (2) is a rough approximation only. It may be that in a single individual it describes tolerably well the relation of the loops in one lead system to those in another. But in another subject the nine coefficients, p, q, r, will have other values. Now this is a practically worthless result. We are far from the ideal to adapt the lead system to the individual. What we need is a set of coefficients which are independent of the subject or patient. Therefore, we must abandon the idea to allow for the accidental peculiarities of body build, inside and outside, and lay all subjects and patients in one and the same vectorcardiographic Procrustean bed. Apart from the individual and accidental varieties, we may hope to find a systematic relation, according to (2), between two lead systems when we compare the vectorcardiograms of a sufficient number of human bodies.

We never can find a set of nine coefficients (p, q, r) that satisfies the equations (2) for all points of the loops of all our subjects. But we must deduce the coefficients that are the best we can obtain. The practical solution is the following: On one pair of loops, frontal and horizontal, in one system for a certain individual we choose a number of corresponding points. Then we try to find the synchronous points on the frontal and horizontal projections of another system (Fig. 5). Each point, say a, has three coordinates that can be measured from the pair of projections in one system, say C, and likewise in the other, D. These 2×3 coordinates, substituted in the equations (2) give three equations, with the nine unknowns, p, q, r. On each QRS loop we have chosen five points, so that they determine its shape approximately. Since each pair of corresponding points gives three equations (2) for the nine unknowns, these five points give $5 \times 3 = 15$ equations. So the number of equations (15) is more than the number of the unknowns (9); the problem is overdetermined. This is still the more true when we consider that there is no reason to restrict the calculation to one individual.

Therefore, we have measured the coordinates of corresponding points on the loops of 150 or more subjects and solved these 150×15 equations with 9 unknowns. It is obvious that this is impossible in the ordinary algebraic sense. In such cases we try to make the best of it. We know that it is impossible to find nine coefficients, p, q, r, which satisfy these more than two thousand equations, but we are con-

tent with the nine values, p, q, r, that give the best, or the least bad, solution, a kind of average over all subjects. What this means exactly may be left unexplained here. May it suffice to say that the classic method of least squares gives a scheme for the calculation, which is easy but tedious to perform. As an example, the average transformation of the Burger into the McFee system is given here:

$$\left.\begin{aligned} X_M &= 0.70\,X_B + 0.22\,Y_B + 0.23\,Z_B \\ Y_M &= 0.04\,X_B + 0.91\,Y_B - 0.16\,Z_B \\ Z_M &= -0.44\,X_B + 0.68\,Y_B + 1.11\,Z_B \end{aligned}\right\} \quad (3)$$

Such calculations make sense only when we draw conclusions from them, and when these conclusions have any effect on our further behavior. The most important conclusion is that in addition to the systematic effect, as found in the way described above, there is a random effect caused by individual differences. In some individuals the average transformation fits quite well so that, for example, after it is applied to a B-loop it gives a loop that gives an excellent agreement with the M-loop. But in other subjects the agreement after transformation is unsatisfactory. Yet the transformation is worth while, since it reveals that the systematic discord expressed by it is of the same order as the random effects.

A second conclusion is that of all transformations that of S in M (or the reverse) is nearest to identity, thus confirming our subjective scores.

It would be well if the transformations could be expressed in a simple geometrical form. This cannot be done exactly; but as a first approximation, B can be obtained from the other systems by a shear. In the American system the downward part of the QRS loop is directed more to the back than in the B system.

We now have added a system that results from the B after transforming it to M. If there were no random individual effects and the dipole were point-shaped, this new system would give results identical to those of the M system. In reality it does not agree so well, but yet the result of the transformation is not so bad. It gives a new B system—we call it B_M—which in the average agrees better with M than does the original B. The scores for the correspondence between B_M and M, as far as we have them now, are almost as good as those for the American systems mutually. Now, when we recognize that in B and B_M only five electrodes are used, this result is remarkably favorable.

What may be the cause of the systematic difference between B and the American systems? It is probable that, for a part at least, it is the assumed heterogeneity in the first system and the assumed homogeneity in the others. Model experiments with different amounts of heterogeneity and numbers of electrode positions in the four systems might contribute to the answer to this question.

The future of vectorcardiography depends on the degree of correspondence and noncorrespondence between different systems. What can we do about it? Can we standardize at this moment? I think one thing is certain: all systems without rational physical foundation must be abandoned. The correspondence among the remaining systems is not bad, even so that some cardiologists say that each of them can be used in clinical practice without serious discrepancies. I fear this is a little bit too optimistic. But in the transformation I described a way is shown for standardization among others by application of a transformation which provides a kind of average.

Let us be optimistic and suppose that in a few years a common opinion has been reached. What then? Is this the end of the task of the physicist in the development of vectorcardiography? I think not. All this was only hunting for the cardiac dipole. But then a much more elusive prey is left, the quadripole and further multipoles. And all of these must be seen as effects caused by the essential electrical processes of which Dr. Weidmann and Dr. Durrer have spoken. So I see a future of intimate collaboration of physicians or biologists with physicists in a time when there will be no longer a sharp boundary between these two groups of scientists.

Development in clinical electrocardiography since Einthoven

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The history of men of science reflects the history of science. Willem Einthoven, a humble, intelligent, and creative thinker, was a great man who was representative of the best in the history of medicine. Unfortunately, most of the history of medicine is a history of errors in a struggle for survival and self-aggrandizement. In the midst of such noncreative activity, occasionally has come a man to advance knowledge and man himself. So it was with Einthoven. The full significance of great accomplishments is only partly realized at any one time, since the significance of great things grows endlessly. A creative development came with the sensitive, accurate, and reliable string galvanometer, a deliberate, methodical, and creative development from the brain of a great and modest man (Fig. 1). Modest and dedicated were even his associates. The early studies of electrocardiography in Einthoven's laboratory were of high quality. History of the subsequent developments in clinical electrocardiography outside Leiden reveals considerable variation in quality of investigations and reports, and reflects more accurately the average state of clinical research and care of patients. As with the writings of great men, those of lesser men reflect and record forever their personalities. May this continue, for then the true history of medicine is recorded, whatever it may be. To select and edit the works of man can only distort the work of man.

Perusal of reports in clinical electrocardiography reveals progress and development resembling that in other medical fields. Among the many contributors to the progress in electrocardiography were a few outstanding minds. Thomas Lewis, James Mackenzie, Alfred Cohn, H. E. Hollmann, W. Hollmann, K. F. Wenckebach, Frank Wilson, Ernest Starling, W. M. Bayliss, Carl Wiggers, Augustus Waller, James B. Herrick, Horatio B. Williams, W. H. Craib, H. C. Burger, and F. Schellong represent a few, in addition to Einthoven himself, who have been the stalwarts of research and development in clinical electrocardiography. Sir Thomas Lewis, who was most responsible for the early developments, was primarily interested in cardiac arrhythmias, whereas F. N. Wilson was the central figure of a slightly later electrocardiographic period who made extremely important contributions to other aspects of electrocardiography.

The history of the development of clini-

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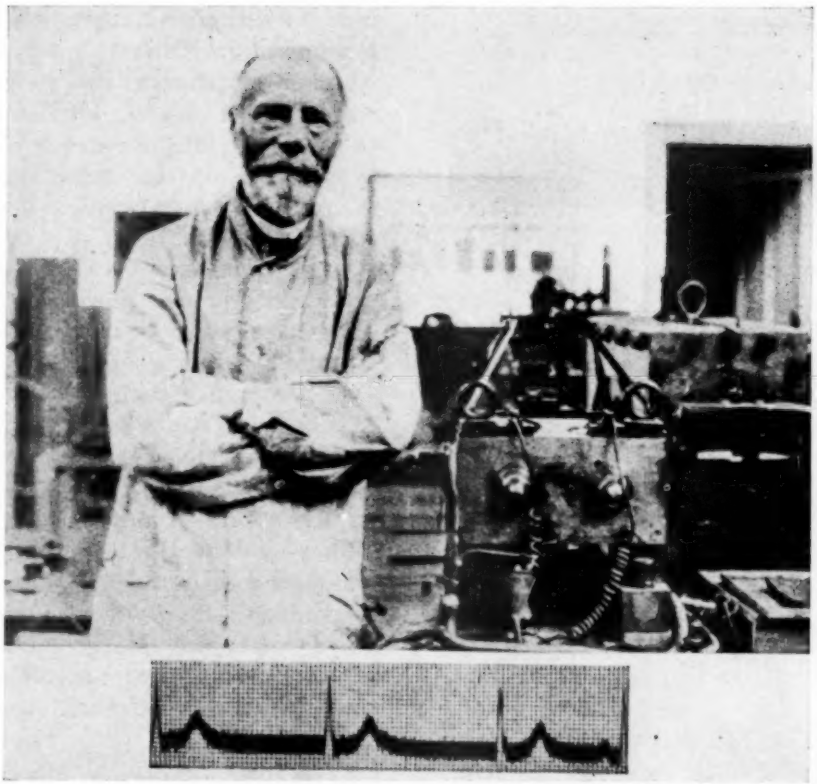


Fig. *1.* Willem Einthoven and his original galvanometer in his laboratory, and a tracing obtained with the equipment. (Reprinted courtesy of Cambridge Instrument Co.)

cal electrocardiography may be divided into the following phases.

1. The period prior to Einthoven, during which time it was shown that electrical phenomena were associated with the heart beat. Studies with the capillary electrometer revealed possible diagnostic alterations in the time course of electrical cardiac events associated with normal and abnormal cardiac states.

2. The period of Einthoven, which resulted in the development of the string galvanometer, the contribution which made clinical electrocardiography possible (Figs. 2 and 3).

3. The period of electrocardiographic study of disorders of the heart beat.

4. The period in which coronary, myocardial, and nonarrhythmic disturbances of the heart were studied, especially coronary heart disease.

5. The period of the introduction of precordial and unipolar leads.

6. Possibly, the period of vectorcardiography.

Prior to Einthoven's time important investigations in electrocardiography had been in progress. The excellent work of Augustus Waller[1-5] and the previous studies of Helmholtz,[6] in 1854, Kölliker and Müller,[7] in 1856, Donders,[8] in 1872, Burdon-Sanderson,[9] in 1880, and others have not been fully appreciated because of the overshadowing influence of Einthoven. The capillary electrometer, though insensitive, difficult to employ, and inaccurate, displayed much information, although it was not always recognized. Its merits were appreciated by those well acquainted with the apparatus and its records. This early work was little appreciated by fellow scientists who were poorly trained, less interested, or ill-informed, and who passed judgment without scientific justification or qualification. Not until Einthoven's galvanometer became available did the value of this early work become obvious. Einthoven's astonishingly excellent recordings were convincing.

It was fully recognized by all cardiolo-

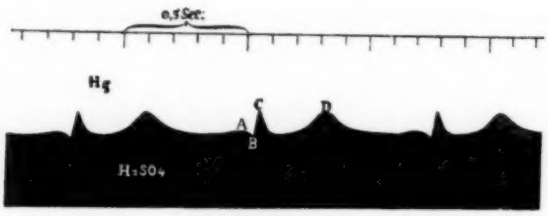


Fig. 1.

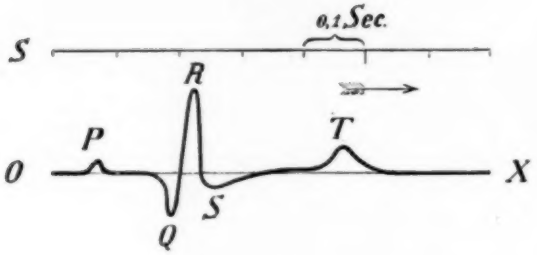


Fig. 2. A recording obtained in 1903 with a capillary electrometer, and a constructed and corrected curve. The latter was a tedious procedure before the string galvanometer. (Reprinted from Einthoven: Pflüger Arch. ges. Physiol. 99:472, 1903.)

gists and the Nobel Committee in Medicine that it was the simple instrument of Einthoven and his clear description of certain theoretical electrocardiographic principles that made clinical and theoretical electrocardiography possible. Soon after the description of the galvanometer in 1903,[10,11] Lewis obtained one[12] and Cohn[13] brought the first electrocardiograph to the United States. Instruments were soon introduced in Germany, Austria, France, and other countries of the world. Interestingly, the first tracings published by Einthoven are still superior to most current recordings obtained by the direct-writing method (Fig. 3).

Because of the great demand for his string galvanometer, Einthoven approached Horace Darwin, youngest son of the biologist and founder of the Cambridge Scientific Instrument Company, Ltd., of London, about the manufacture of his instrument. Darwin agreed, and Einthoven worked as advisor to the company until his death in 1927.[12] The instrument was immediately simplified and made smaller. The first unit built by Cambridge was completed in 1911. By the outbreak of World War I, thirty-five had been supplied for clinical and research purposes.

The first electrocardiograph ever placed into operation in North America was an Edelmann instrument made in Germany, which Alfred Cohn brought to the U. S. A. with him for use at the Rockefeller Institute for Medical Research in the summer of 1909. This electrocardiograph is now in my laboratory at the Tulane Medical School (Fig. 4).

Cohn had spent the preceding spring and summer in the laboratory of Sir Thomas Lewis. The electrocardiograph installed in Lewis' laboratory at that time was also an Edelmann unit which had been purchased in 1908.

The first string galvanometer made in America was a type "A" ordered by Cohn in the fall of 1914. It was designed by Professor Horatio B. Williams, and constructed by Charles F. Hindle, a mechanic in the workshop of the old College of Physicians and Surgeons, West Fifty-ninth Street, New York City. This galvanometer was delivered to Cohn at the beginning of May, 1915. The galvanometer for this electrocardiograph is now on display in the Smithsonian Institute in Washington, D. C. The first tracing obtained with the new type "A" galvanometer was recorded on May 20, 1915, on Mr. Joseph Webb.

The first paper published on electrocardiography in the United States was "The Electrocardiogram in Clinical Medicine" by Walter B. James and Horatio B. Williams, which appeared in the *American Journal of the Medical Sciences*, November, 1910.

It was in large measure because of the high standards of ethics in the manufacture, research, development, and marketing of these early machines that electrocardiography had such sound and successful growth. Functionally poor and unreliable production could have destroyed electrocardiography in its early days. The manufacturers have made and continue to make most significant contributions to electrocardiography (Fig. 5).

About 1928, Cassidy and Hall[12] developed the first portable electrocardiograph. It weighed 80 pounds. In 1936, a portable instrument which weighed 30 pounds and used electronic methods was introduced. The first direct writer was introduced at Cambridge, England.[12]

New portable apparatuses (Fig. 6) have been developed and are now marketed at prices which make the electrocardiograph available to the individual doctor. Then followed the "direct-writer" portable electrocardiograph which is found in almost every doctor's office in the United States today. With the increase in the number of electrocardiographs sold, not only the use but also the abuse of electrocardiography has increased in clinical practice.

Einthoven[10,14-18] made some of the important original clinical electrocardiographic observations (Fig. 7). He noted that inspiration increased heart rate and that expiration decreased it. He described the wave patterns in normal man, the changes associated with respiration in the QRS complex in Lead III, and the influence of cardiac position on the electrocardiogram. He described the U wave in normal man, published tracings of patients with left ventricular hypertrophy, right ventricular hypertrophy, subacute bacterial endocarditis, myocardial degeneration, and pericarditis. Einthoven described the first electrocardiogram showing dextrocardia with situs inversus viscerum[16] with and without the right and left arm electrodes reversed. His classic report with Fahr and de Waart[16,17] on the principle and method for calculating the electrical axis at any time in the electrical cycle attests his interest in, and knowledge of, theoretical electrocardiography. This method is still used to great advantage today in both clinical and experimental electrocardiography. Einthoven and his associates demonstrated the use of the electrocardiogram for the timing of mechanical cardiac and pulsatile events.[19] That the electrocardiogram played an early and major role in physiologic and clinical studies is probably due to Einthoven's early and intense in-

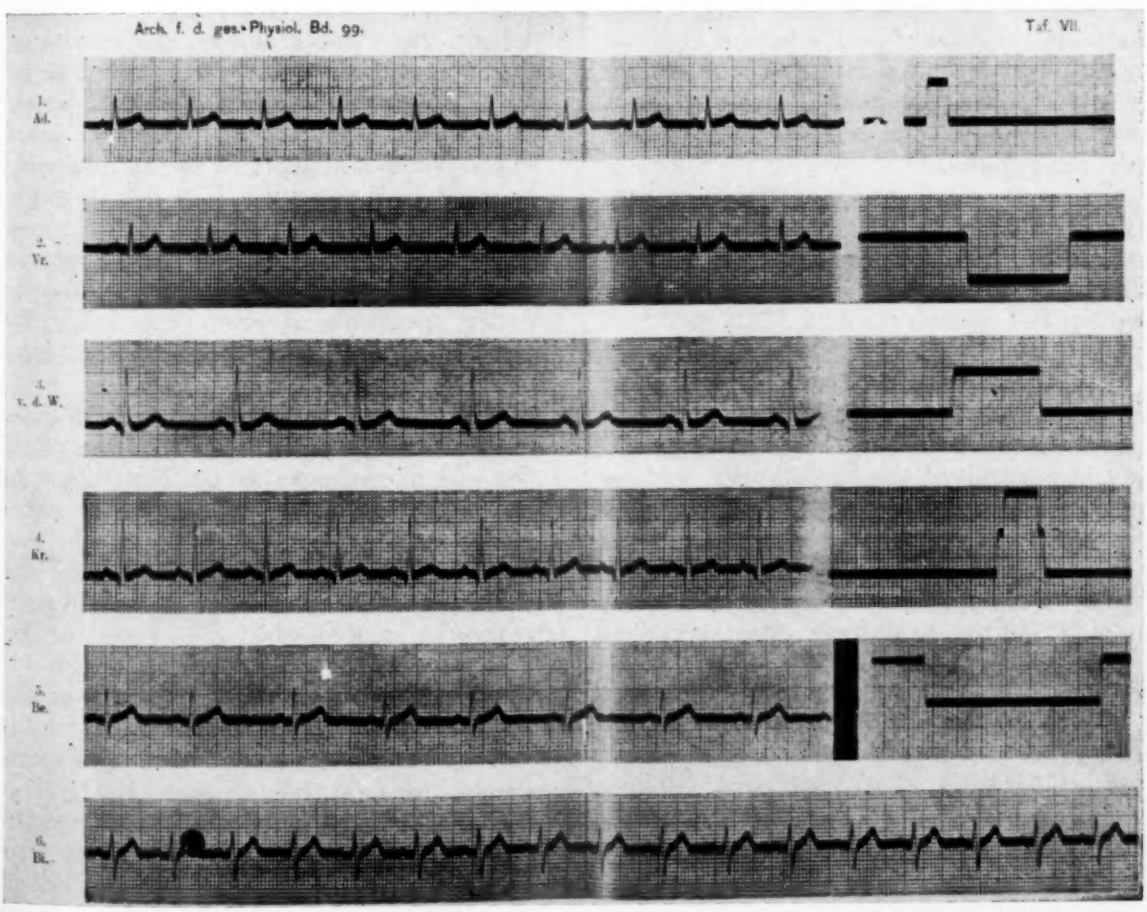


Fig. 3. Several electrocardiograms obtained by Einthoven, showing the excellence of the records obtained with his original electrocardiograph. (Reprinted from Einthoven: Pflüger Arch. ges. Physiol. 99:472, 1903.)

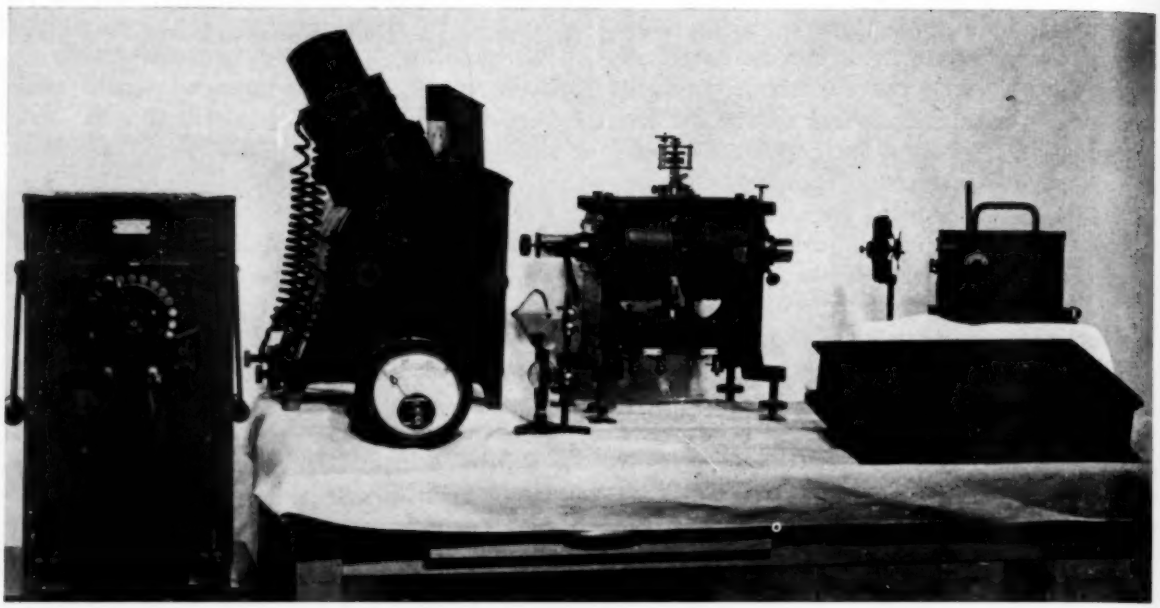


Fig. 4. The first Edelmann electrocardiograph used in the U.S.A., which was brought to this country by A. E. Cohn in 1909. It is now at the Tulane Medical School in New Orleans. The various parts of the electrocardiograph were placed on a table for this photograph.

terest in the clinical and practical applications of his apparatus, no doubt attributable in part to his own medical training as a doctor of medicine and to his father's experiences as a practicing physician.

Although Einthoven's clinical applications of the string galvanometer were relatively few compared to those of Sir Thomas Lewis, of London, they were timely and of high quality. Einthoven was a physiologist and not a clinician. He recognized Lewis' contribution when he stated in his Nobel lecture that had it not been for Lewis' work he probably would not have received the Nobel prize, because only a few people would have recognized his electrocardiograph as a useful clinical tool.

Lewis (Fig. 8) conducted an intensive, orderly, deliberate, and objective investigation of disorders of the heart beat. He established clinical investigation as sound research and showed the scientific world, as Mackenzie had done previously, that important fundamental research can be performed on man. Lewis worked with the Einthoven string galvanometer, which was destined to record repeatedly discovery after discovery.[20-40] He worked in limited space under a stairway in the basement of the University College Hospital Medical School. He cleverly localized the site of the normal pacemaker of man and of dogs[25-27] by investigating the time course of the depolarization process in the heart of the dog and sharply localizing the point of origin of the impulse. The details of the time course of the depolarization process are a most important and still unsolved aspect of electrocardiography. This is under excellent investigation today by D. Durrer of Einthoven's country, Holland.[41,42]

It might be of interest to digress for a moment to illustrate the importance of the electrocardiograph of Einthoven in locating the sinoauricular node or pacemaker of the heart. The history of these studies shows the interrelationship of the interests, work, and methods of investigators in science which can result in important discoveries. For example, Martin Flack as a young medical student at the London Hospital visited his good friends Dr. and Mrs. Arthur Keith at their farmhouse, Mann's Place, near Bredgar in Kent[43] during his summer vacation of 1906. The Keiths had converted their study into a private laboratory which contained a collection of hearts from all sorts of wild and domestic animals of the area, and had plans to verify and extend

the significant discovery of the A-V node by Tawara. One hot summer afternoon, Dr. and Mrs. Keith decided to ride their bicycles and left Flack in the laboratory to cut serial sections of a paraffin-embedded heart of a mole.

Upon their return, Flack was in a state of excitement over the discovery of a strange mass of muscle-like structure near the junction of the superior vena cava with the right atrium. It resembled the node of Tawara and was later shown by Keith and Flack to exist in the same place in the hearts of all of the other mammals. They assumed this to be the source of the cardiac rhythm of the heart.

In 1910, Lewis, [25-27] in brilliant experiments with his new electrocardiograph, showed in the dog that this special tissue remained *negative* to all depolarization processes of the atrium regardless of the direction of movement of the wave fronts which he recorded with his bipolar leads placed on the atria (Fig. 9). The Oppenheimers then showed that this site of primary negativity was the special tissue described by Keith and Flack, thus identifying the node of Keith and Flack as the site of origin of the impulses of the heart beat.

As Lewis demonstrated, the galvanometer did not require much space, and since the recordings were physically good, clear, and permanent, well-designed experiments could be planned to answer important questions under relatively unfavorable working conditions. It was and still is possible to perform excellent clinical and experimental electrocardiographic research under a stairway if one is capable of asking the pertinent questions and designing the proper experiments. Lewis possessed the advantages of mental and physical vigor, a good electrocardiograph, curiosity, neatness and simplicity in experimental design, and clear, analytical thinking.

When Lewis began his studies in electrocardiography, Mackenzie was engaged in his classic work on cardiac irregularities, using his relatively cumbersome and difficult polygraph. Lewis began his studies of cardiac irregularities using the Mackenzie type of polygraph. However, unlike Mackenzie, who was reluctant to accept the electrocardiograph, Lewis quickly and wisely recognized the electrocardiograph as a powerful tool, especially suited for the study of cardiac irregularities. Although Mackenzie had established the importance of irregularities of the heart beat in clinical medicine, Lewis rapidly advanced and consolidated the state of knowledge. By means of the electrocardiograph he described the mechanism of important cardiac irregularities, defined the pathologic physiology, and established diagnostic and prognostic criteria, treatment, and incidence[24,31-34,36,37] of the major disorders of the heart beat. He provided an excellent background for research by others, so that the less common and more complicated irregularities could be readily recognized. New ones are still being described each year.

Lewis published about 100 lengthy, detailed papers and three excellent monographs[27,29,30] on disorders of the heart beat

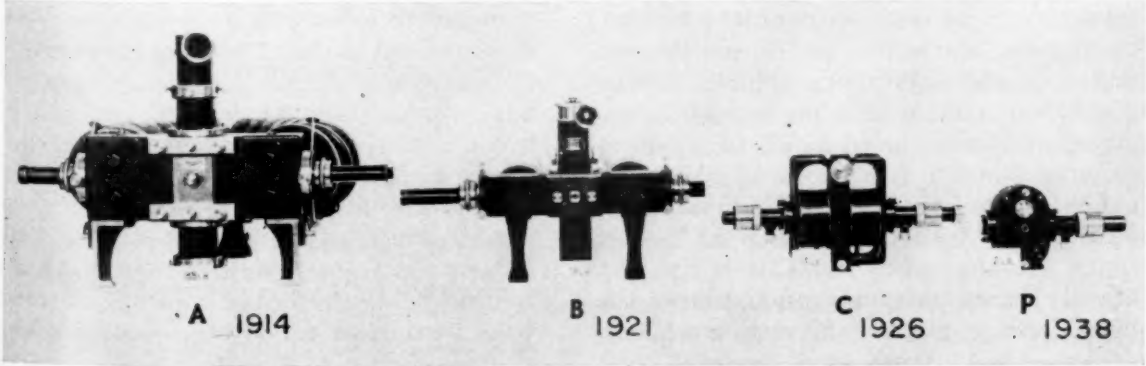


Fig. 5. Progressive developments (1914-1938) in the string galvanometer, showing the great reduction in size with successive models. (Reprinted courtesy of Cambridge Instrument Co.)

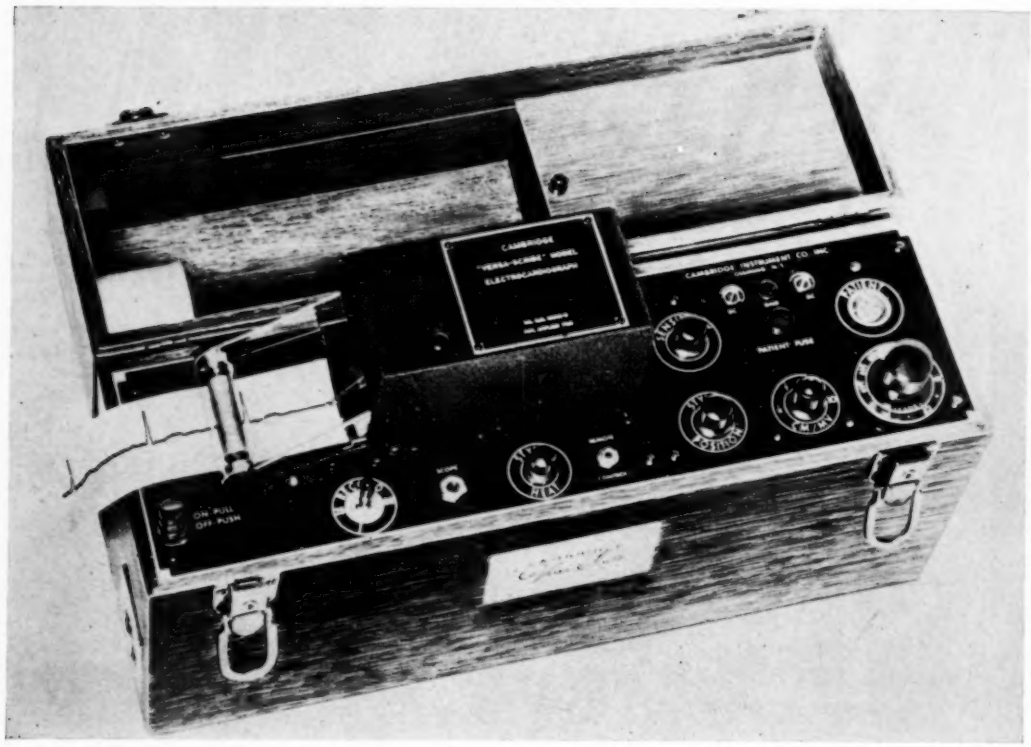


Fig. 6. The present-day model of the portable direct-writer electrocardiograph. Compare with Fig. 1. (Reprinted courtesy of Cambridge Instrument Co.)

in which the electrocardiograph was shown to be the instrument par excellence. He bridged the period of the polygraph and the period of the electrocardiograph. His small book, *Clinical Disorders of the Heart Beat*,[30] should be read by every physician, and certainly by anyone who undertakes to interpret electrocardiograms clinically. Lewis made very few mistakes in his great volumes of fine work. He was the first of the great clinical investigators to demonstrate to the biologists and basic scientists that excellent, fundamental, methodical research can be done on man, the highest of animals. Mackenzie and Lewis showed that man is a laboratory animal. It was Einthoven who made this possible. Few biologists have equaled Lewis in scientific accomplishment.

Lewis stated as early as 1912,[22] only nine years after Einthoven's original paper, that "the time is at hand, if it has not already come, when an examination of the heart is incomplete if this new method is neglected." It must have been a great satisfaction to Einthoven to see over 100 excellent papers appear from one man which demonstrated more and more the clinical importance and indispensibility of his galvanometer. Lewis' book, *Mechanism and Graphic Registration of the Heart Beat*,[27] which appeared in 1920, and reached a third edition by 1925, summarized his work for the world and was the first great book on electrocardiography.

Lewis later shifted his interest from electrocardiography to clinical peripheral vascular physiology. With this change in research interest the third era in clinical electrocardiography ended, because there remained no one especially interested in an organized, orderly study of disorders of the heart beat. Many people subsequently have studied isolated problems of cardiac irregularities and have advanced the field, establishing electrocardiography even further as the best method for the study of cardiac irregularities. However, no one has yet equaled Lewis' scientific productivity in this field. Einthoven and Lewis must have been great friends and mutual scientific admirers.

The activities in electrocardiography during the first decade or two after the

description of the string galvanometer were concerned primarily with a few selected applications of the instrument. An important effort was that of educating clinicians, clinical investigators (a newly emerging type of investigator), and physiologists with the use of the electrocardiograph and its many advantages for the study of the time course of electrical events associated with the heart beat of man and other animals. The clinical applications of the electrocardiograph were then limited to a few centers; general clinical use came much later.

The fourth era in clinical electrocardiography began in 1912, when James B. Herrick,[44] of Chicago, clearly described the clinical syndrome of myocardial infarction and angina pectoris. He recorded an electrocardiogram on a patient with coronary disease and pointed out QRS and T-wave changes associated with these diseases (Fig. 10). The normal patterns of the electrocardiogram were fairly well established by 1919, when Herrick[45] published his classic paper which vividly described the clinical syndrome of coronary occlusion and myocardial infarction so that people began to die of myocardial infarction rather than "indigestion."

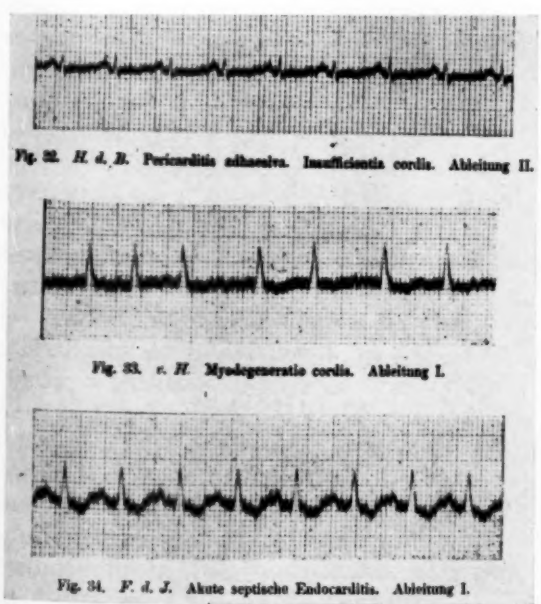


Fig. 7. Electrocardiograms for several diseases in man, published by Einthoven in 1908. (Reprinted from Einthoven: Pflüger Arch. ges. Physiol. 122:517, 1908.)

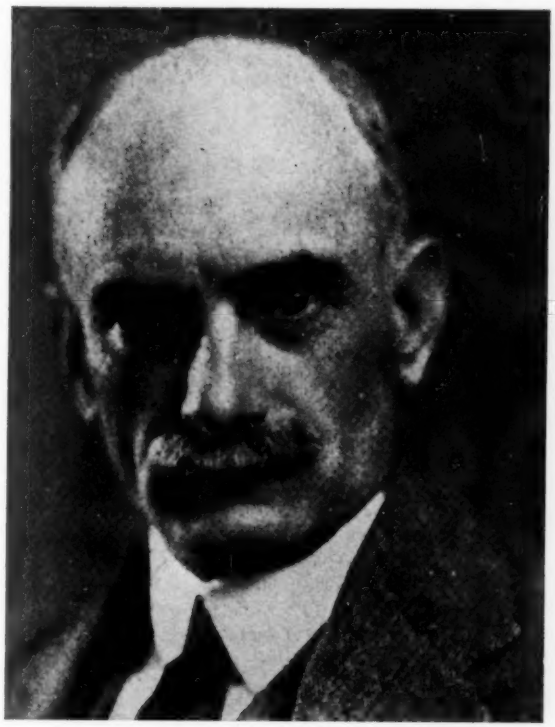
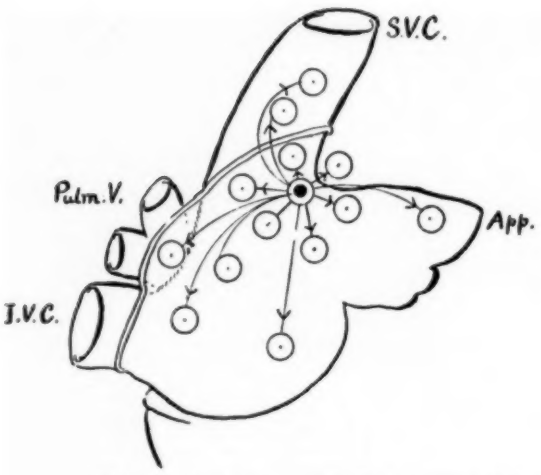


Fig. 8. Sir Thomas Lewis. (Reprinted from Burch: *A Primer of Cardiology*, Philadelphia, 1953, Lea & Febiger.)

Herrick[45] suggested to Fred Smith that he study the electrocardiographic and anatomic changes in the hearts of dogs after ligation of the coronary arteries.[46-48] Herrick, Smith, and others established the electrocardiograph as a useful instrument for the study of cardiac disturbances other than disorders of the heart beat. Pardee[49-54] described the "coved" or ischemic T wave, the Q-T pattern, and other electrocardiographic changes associated with myocardial infarction. This aroused considerable interest in electrocardiography, especially when it became possible to recognize myocardial infarction and angina pectoris in the living patient. The electrocardiograph began to serve as the objective graphic method for establishing firmly and convincingly the clinical diagnosis of coronary heart disease. Those who had considered the electrocardiograph to be merely an improvement over the polygraph for the diagnosis of irregularities in cardiac rhythm and not otherwise an especially important clinical instrument began to realize that it recorded important phenomena which the polygraph was incap-



The contacts as applied to an auricle. The central contact, which is invariably relatively negative to outlying points when activity in the auricle starts, overlies the *S.A.* node.

Fig. *9*. Diagram from Lewis' paper, showing his localization of the site of the S-A node in the dog by means of the electrocardiograph. (Reprinted from Lewis: *Lectures on the Heart*, New York, 1915, Paul B. Hoeber.)

able of detecting. This new application excited the curiosity of many and convinced even the skeptics that the electrocardiograph had far-reaching potentialities in clinical medicine.

Bousfield,[55] in 1918, initiated clinical interest in the electrocardiographic changes in angina pectoris with the publication of the first tracing recorded during an attack of angina pectoris (Fig. 11). Ten years later, Feil and Siegel[56] recorded the electrocardiogram on patients during attacks of angina pectoris (Fig. 12) and showed S-T-segment and T-wave changes during the episode of pain. These observations were quickly repeated and elaborated upon by others, so that the electrocardiogram was soon shown to be useful in the diagnosis and management of angina pectoris. Feil demonstrated his tracings to Sir Thomas Lewis, when the latter was lecturing in the United States[31] and aroused Lewis' interest.

The electrocardiogram was studied further both clinically and experimentally[57-82] in order to learn more of its value in coronary artery disease. It was shown to be useful in following in detail the progress of healing of infarcts, as well as important, subtle, subclinical changes in ischemic heart disease.

Master and Oppenheimer[70] introduced the two-step test as a procedure for measuring mechanical cardiac efficiency. Master wrote on this phase of the test for a number of years before he suggested its use as a method to precipitate attacks of angina pectoris and the associated diagnostic electrocardiographic changes.[83] Levy[68] introduced the anoxia test for the same purpose. These tests extended further the clinical applications of electrocardiography.

Lewis[25,27,28,39,40] had recorded the electrocardiogram with electrodes placed directly upon the epicardium. Wilson had also been interested in similar studies.[74,84-91] Neither, however, had shown the clinical usefulness of leads obtained with electrodes placed over the precordium or elsewhere on the surface of the chest. Nevertheless, their experiments initiated the next era in clinical electrocardiography. It was Wolferth and Wood who first effectively and convincingly demonstrated the clinical value of the precordial lead in the diagnosis of myocardial infarction.[81,82] They introduced a new lead, the apical or fourth lead, to clinical cardiology. The clinical value of this lead was so well established by these investigators that, when their paper appeared, many other clinicians immediately began to repeat these studies and to introduce chest leads of their own. Reports began to appear at such a rapid rate, with so many different reasonable and unreasonable suggestions for recording the special leads, that only a few physicians were able to follow the ideas. This led to such confusion that a special committee was appointed by the American Heart Association and the Cardiac Society of Great Britain and Ireland to standardize the chest leads. The committee's recommendations in 1938[92] immediately halted the confusion. It is interesting to note, however, that, as with many committee decisions, the recommendations were so much influenced by prejudices and subjective factors of the time that all members of the committee except one failed to recognize the importance of the central terminal of Wilson and his unipolar lead concept[85,87] which were already strongly taking root in many of the better electro-

cardiographic laboratories. The superiority of this lead system is evident from its general use today. In time, accomplishments eventually reach their proper level. This one achieved its level quickly and within the lifetime of the members of the special committee.

With the advent of multiple precordial leads, unipolar limb leads, and augmented unipolar limb leads,[93,94] clinical electrocardiography entered its fifth era. These new leads are useful not only in the diagnosis and management of cardiac irregularities but also in the diagnosis and management of diseases of the myocardium, pericardium, and endocardium, as well as of diseases of the aorta and noncardiac organs which indirectly disturb the heart. The augmented unipolar limb lead[93,94] has its value in making simple the construction of a selector switch for the present-day electrocardiographs.

It would be impossible to discuss all of the numerous advances in clinical electrocardiography which resulted from the use of precordial leads.[95,96] Precordial leads are an indispensable part of conventional clinical electrocardiography.

During the third, fourth, fifth, and early sixth decades of this century, important advancements were made in theoretical electrocardiography[97,98] and in training and education in the field. Wilson and his associates published many important papers[69,74-80,85-91,96,99-113] which clarified existing concepts in electrocardiography and introduced new ones. Wilson introduced the concept of the ventricular gradient,[89] one of his most important contributions (Fig. 13). This concept was developed by Ashman,[114-124] and its clinical usefulness was extended by other investigators. Unfortunately, the ventricular gradient has not yet received the attention it deserves. It will, when satisfactory integrating circuits are developed to eliminate the tedious manual calculations presently obtained from conventionally recorded electrocardiograms.

It was not until 1932,[112] that the electrocardiographic patterns for the diagnosis and differentiation of right and left bundle branch block were clarified in studies in dogs by Wilson, Macleod and Barker. They and others showed with theoretical and pathologic[125] data that the presently ac-

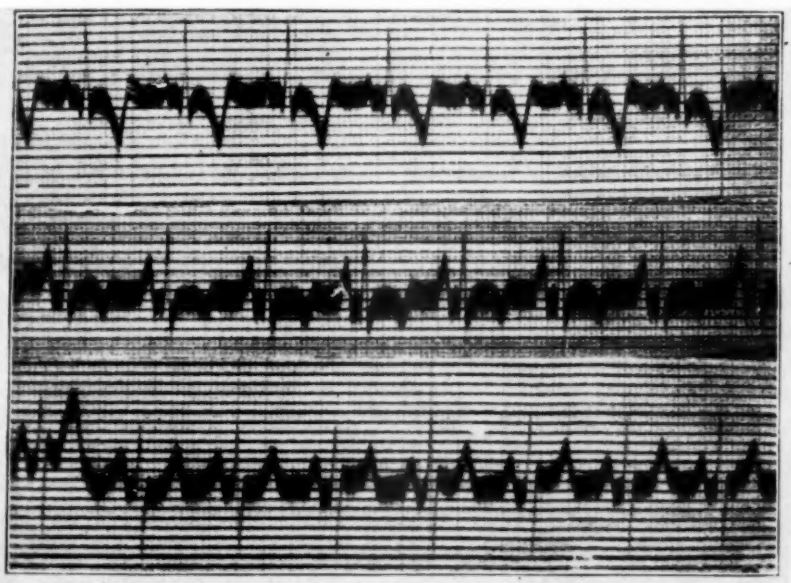


Fig. 3 (Case 3).—Electrocardiogram taken May 3, 1917, forty-one days after the coronary obstructive symptoms. Digitalis not used at this time.

Fig. *10*. Tracings published in 1919 by James B. Herrick in his classic paper describing the clinical syndrome of coronary occlusion. (Reprinted from Herrick: J.A.M.A. 72:387, 1919.)

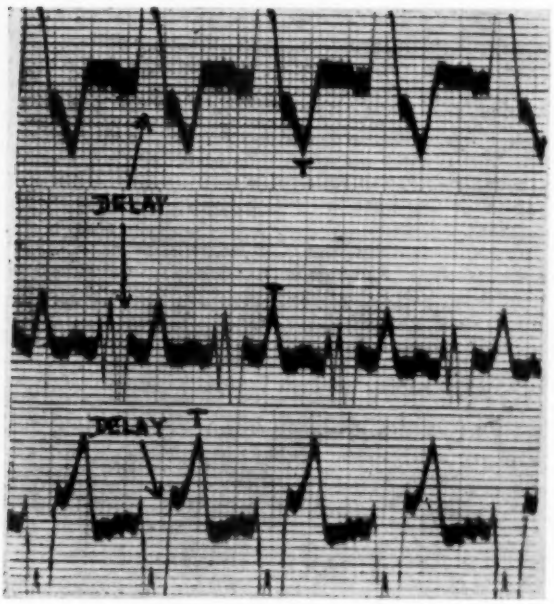


Fig. *11*. The first published tracings on a patient with angina pectoris. (Reprinted from Bousfield: Lancet 2:457, 1918.)

cepted diagnostic electrocardiographic criteria are correct for complete bundle branch block. It may be added parenthetically that there are still many unsolved problems in the field of disturbances in conduction.

Recently, there has been a significant and rewarding entrance of physicists, biophysicists, engineers, and mathematicians into the field of experimental and theoretical electrocardiography. Professor H. C. Burger, like Einthoven, a Dutchman, has made and is still making important fundamental advances in electrocardiography.[126-130] His lucid, concise, modest, and important contributions have received the recognition of all investigators in electrocardiography. These are appreciated by all who are engaged in a serious study of electrocardiography.

Hubert Mann,[131-134] of New York, introduced the concept of the monocardiogram (Fig. 14) in 1920, and reported on the subject on several occasions. He even introduced a special mirror galvanometer activated by three electromagnetic coils[133] to record the monocardiogram mechanically. His work was ignored for about 15 years until Wilson and his associates,[104-106] Schellong[135-139] (Fig. 15), and Hollmann and Hollmann[140,141] independently and essentially simultaneously introduced the cathode-ray oscilloscope to record the monocardiogram which they independently renamed the vectorcardiogram.

During World War II, only a few investigators[95,119,142-152] studied the vectorcardiogram. Once the war was over, interest in the field of vectorcardiography increased. A considerable number of papers on the subject followed.[146,147] As with the precordial leads a decade before, opinions varied widely concerning the technique and electrode placement in, and clinical significance of, spatial vectorcardiography.[148-152] This discordance has impaired the clinical, but not necessarily the scientific, development of vectorcardiography. With continued study and more extensive clinical use of spatial vectorcardiography, its clinical possibilities are becoming established. Although it will not replace conventional clinical electrocardiography, it does supplement it. Once fully established as clinically useful, the adoption of vectorcardiography will establish the sixth era of clinical electrocardiography. This era has not yet arrived.

The present rapid development of computer analysis of clinical data includes electronic interpretation of electrocardiographic data. This may eliminate some of the gross errors in the interpretation of electrocardiograms made by ill-informed clinicians. Although appearing complicated at first glance, the use of electronic computers in electrocardiographic interpretations needs and is receiving diligent study today.

With man's penetration into space and the associated advances in telemetering physiologic data over great distances the electrocardiograph has entered a new field of research and application. When the United States Army's Research Division sent the two monkeys 300 miles into space and back safely, the electrocardiograph was used to record during flight every heart beat and to follow in minute detail the behavior of the two hearts.[153] Electrocardiography continues to spread into new fields of study.

It is impossible to emphasize adequately the developments and contributions of each person to clinical electrocardiography. Lewis' book[27] summarizes the important work up to 1925. Other monographs[154,155]

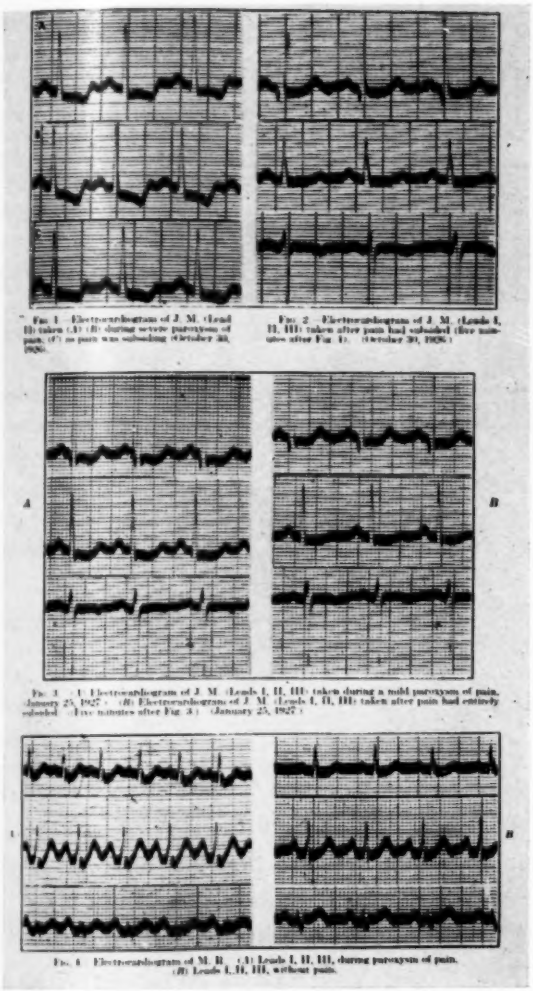


Fig. *12.* One of the first published electrocardiograms obtained on a patient during an episode of anginal pain. (Reprinted from Feil and Siegel: Am. J. M. Sc. 175:255, 1928.)

and reviews[156] indicate advances since that period. Reference must be made to these publications in order to appreciate the importance of the many developments and the work of the many contributors. Furthermore, electrocardiography has been applied to many clinical states, and new ones appear regularly. Newer clinical applications include a study of electrocardiographic changes produced by disturbances in electrolyte metabolism, lesions of the central nervous system, alcoholism, metabolic disturbances, and others too numerous to mention.

The electrocardiogram and electrical cardiac events have been extremely useful in other clinical problems, such as the timing of murmurs and mechanical events of the heart beat (Fig. 16) and the precise triggering of apparatus.[19] The electrocardiogram has been used to monitor the heart during cardiac catheterization, pericardiocentesis, anesthesia, cardiac surgery, quinidine therapy, electrolyte therapy, treatment of systemic medical emergencies, and physiologic and pharmacologic experiments. No clinical center or physiologic laboratory of any importance is without access to an electrocardiograph, and many have several, including multichannel recorders in everyday use for clinical or research purposes, or both.

The clinical developments in electrocardiography illustrate the historical developments in any clinical procedure. The major development of Einthoven, the string galvanometer, was described in 1903. Its importance was realized by only a few investigators, who immediately began to exploit its possibilities to answer important questions. Other investigators seemed to have resisted the electrocardiograph, probably because their course of investigations of the heart had suddenly become archaic. Most people were not even aware of Ein-

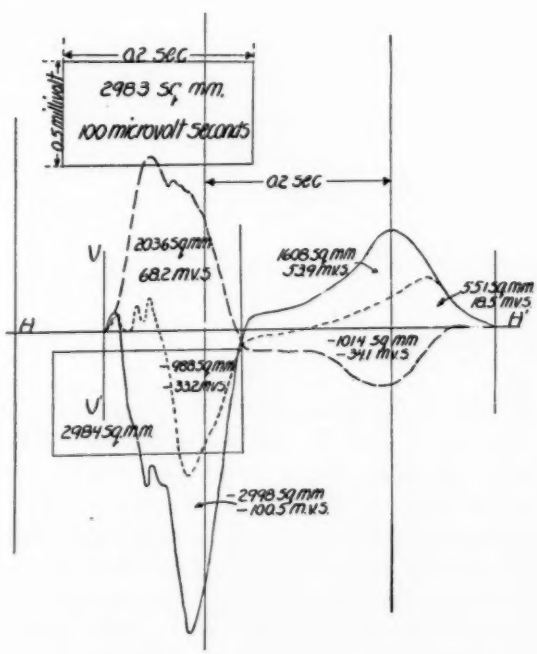


Fig. *13.* An illustration obtained from the original and classic paper by Wilson and associates on the ventricular gradient. Tracings of ventricular complexes. Area measurements were made with a planimeter. (Reprinted from Wilson et al.: Am. Heart J. 10:46, 1934.)

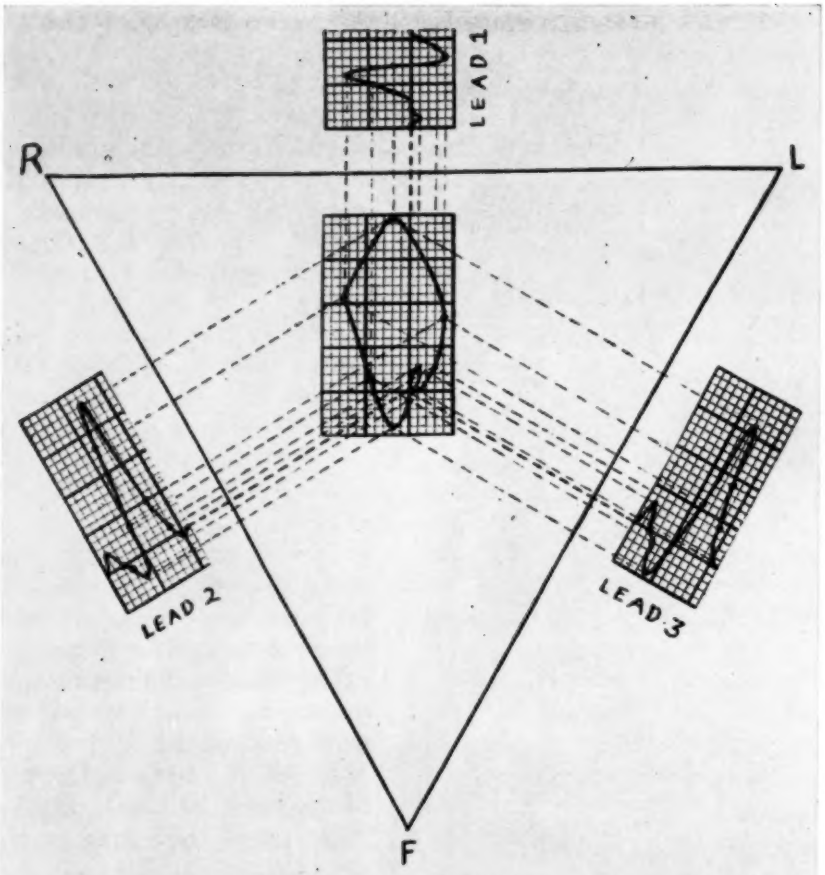


Fig 2.—This figure shows the monocardiogram which is derived from an electrocardiogram published by Einthoven (Fig. 8).[1] It can be seen that the three leads of the electrocardiogram are really derivatives of the monocardiogram, obtained by successive projections of the monocardiogram on the three sides of the equilateral triangle.

Note that in this monocardiogram, as in all the others shown in this article, the right side is on the observer's left. This is in accordance with ordinary cardiographic usage as regards Einthoven's triangle and facilitates interpretation.

Fig. *14*. A monocardiogram (vectorcardiogram) drawn from one of Einthoven's published electrocardiograms. (Reprinted from Mann: Arch. Int. Med. 25:283, 1920.)

thoven's announcement and surely did not appreciate its importance. Nevertheless, through the mature leadership and guidance of a few investigators the electrocardiograph was put to good use, and the great potential of this clinical and research tool was gradually brought to the attention of more and more people in physiology and clinical medicine. Older methods of study were discarded and the new one was accepted.

During the course of the developments of electrocardiography it was most fortunate that Einthoven used the two hands and a foot of his subjects as the points of electrode placement. Einthoven, de Waart and Fahr[16] introduced the concept of the equilateral triangle as a convenience for theoretical electrocardiographic analyses, and although it has been shown by Burger and his associates[126-130] to be inaccurate, the method of electrode placement and the concept were fortunate for clinical electrocardiography. The system of electrode placement was so simple that doctors and technicians everywhere were able to make reliable, reproducible, and comparable recordings with little difficulty.

Had a complicated reference system been introduced, clinical electrocardiography would have been retarded. Anyway, no reference frame can be perfect. Arrighi,[157-159] in 1939, introduced a different and interesting reference frame, but this could not be expected to replace the simple, reliable, and reproducible one used today throughout the world.

Wilson and his associates and students were the first after Einthoven made his initial theoretical investigations[16] to study methodically the theoretical aspects of electrocardiography.[160] Although not strictly clinical in nature, these studies placed electrocardiography on a sound foundation and were responsible for important clinical advancements. There has been an increase in interest in the last 10 years in this type of theoretical, physical, and mathematical approach to problems in electrocardiography, with more physicists, engineers, biophysicists, and mathematicians working in the field than ever before. These investigations have assisted the clinical applications.

An important nonclinical electrocardiographic advancement which has influenced, and will continue to influence, clinical concepts in electrocardiography was made by Woodbury and Woodbury[161] when they introduced a very simple microelectrode technique for the study of the time course of variations in membrane potential of a single fiber of mammalian heart muscle. Weidmann,[162] of Switzerland, and Brooks, in the United States, have been making especially important contributions in this field. These studies have had considerable influence upon clinical electrocardiography.

Within recent years there has been greater interest among the more sophisticated university "heart stations" in the electrophysiologic explanation for the alterations produced by cardiac disease. Schellong[139] illustrated very nicely the application of the concept of monophasic action current to an explanation of the effects of digitalis on the T wave and the T-wave changes due to myocardial disease. Theoretical and experimental investigations have become an essential part of the routine operation of the heart stations of

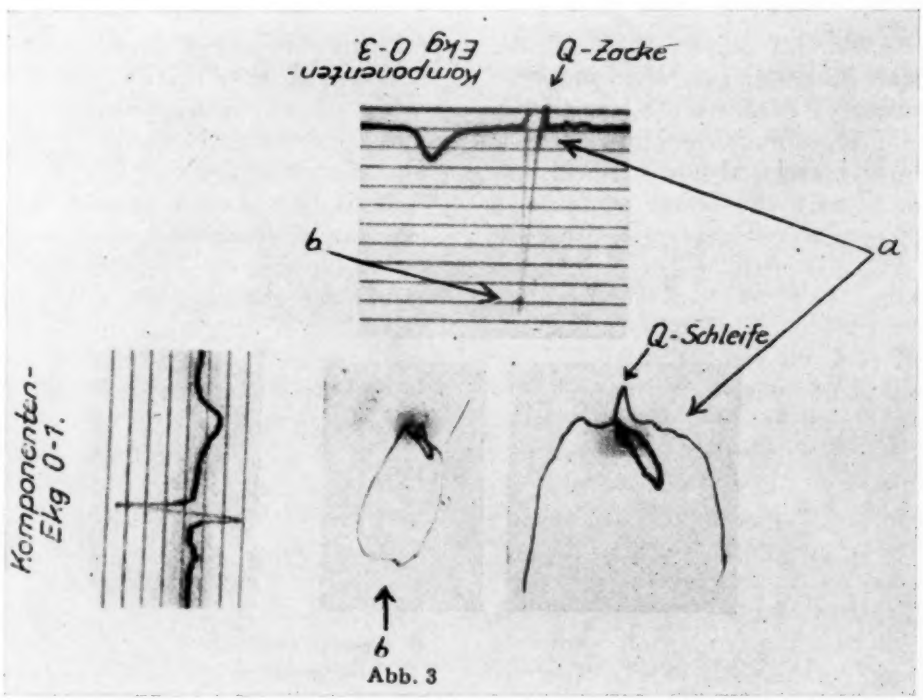


Fig. *15*. A vectorcardiogram recorded by means of the cathode-ray oscilloscope, a relatively new electronic device in 1937. Wilson,[105] Hollmann and Hollmann,[141] and Schellong[136] published the same idea almost simultaneously. (Reprinted from Schellong: Ztschr. Kreislaufforsch. 29:498, 1937.)

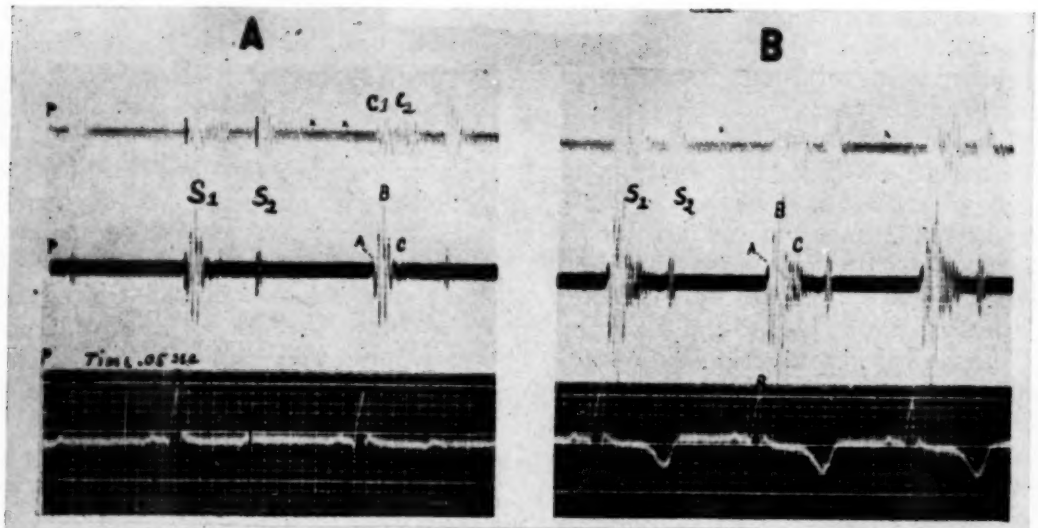


Fig. 4. Record showing aortic sounds (upper curve), right ventricular sounds (middle curve) and relation to EKG, lead II. A, during hypodynamic heart action consequent to opening chest; B, during action of adrenalin (one-half actual size).

Fig. *16*. Illustration showing early use of the electrocardiogram to time cardiovascular mechanical and hemodynamic phenomena. (Reprinted from Wiggers and Dean: Am. J. Physiol. 42:476, 1917.)

medical schools and university hospitals. Through the efforts of many workers the electrocardiogram was studied in experimental animals and in normal and diseased man and was correlated with clinical and autopsy data, with the ultimate objective of developing its clinical application to the maintenance of the health and happiness of man. Its clinical usefulness is fully established today, probably far more extensively than once thought possible by Einthoven and the early workers.

With the clinical use of the electrocardiograph at the bedside of patients and in the offices of doctors all over the world, interesting behavior in cardiac mechanism and electrical phenomena under various circumstances of cardiac disease and therapy have been recorded. Ventricular fibrillation, ventricular tachycardia, complete heart block, conduction defects, the behavior of the heart in dying people, in anesthetized people, in patients in severe circulatory collapse, in cardiac pain, in cardiac tamponade before, during, and after pericardial paracentesis, in exercise, fainting, attacks of angina pectoris, coma, operations, defibrillation, and in many other clinical and physiologic conditions and circumstances have been observed electrocardiographically.

It is not always possible to ascertain accurately when the descriptions of specific electrocardiographic observations were first published. For example, the first published recording of ventricular fibrillation in a patient who survived is shown in Fig. 17. It is interesting to note that Einthoven published some of the first electrocardiograms in various types of cardiac disease. Cremer,[163] in 1906, apparently was the first to record simultaneously an electrocardiogram of the fetus and the mother (Fig. 18). Incidentally, the obstetrical applications of electrocardiography have not been fully developed.

Wilson and associates[76] were the first to show that filling the stomach with cold water lowered the T wave in the electrocardiogram. This report as well as those from other laboratories emphasized the importance of considering the marked vari-

ations that can occur in the electrocardiogram of a normal person when he is subjected to relatively minor environmental stress. These factors are always considered in good electrocardiographic laboratories.

The practicing physician was assisted in the clinical developments in electrocardiography by the physiologist, although mainly by a relatively new kind of clinician, the clinical investigator. It was the latter who made the greatest contributions and major advances in electrocardiography since Einthoven. Electrocardiograms were published early for the goldfish, frog, tortoise, and pigeon (Fig. 19), for the dog with and without chloroform and with and without intact vagi, for the snail's heart with and without $CaCl_2$, of the first beats of the chick embryo,[164] and for many other animals and circumstances. These early recordings were most important because they clearly demonstrated the wide range of applicability of the Einthoven galvanometer in research and its great potential for the study of normal and diseased hearts. Experimental studies on animals provided a better understanding of electrocardiographic problems in man.

The course of the development of clinical electrocardiography was not a smooth one. It had to progress within an environment created by man. The prejudices and selfishness of men actively and passively obstructed its path. The greatest interference originated from those with the least knowledge of the subject and from those who were strongly opinionated. For example, a medical club is said to have existed in Boston, which may still exist today, that had as its only constitutional requirement that electrocardiography was not to be mentioned in its meeting, not even a T wave. Fortunately for the freedom of man such a club can exist, but such attitudes muzzle freedom of scientific thought and discourse. The general ridicule and expressions of pessimism by the least informed were certainly heard widely. With the firm convictions and perseverance of the leaders and of those less well known, electrocardiography continued to develop, until it has now reached a state at which even the greatest skeptics wish to know the electrocardiographic manifestations when they, themselves, develop coronary disease.

The proper recording of the electrocardiogram offers no difficulty, and an electrocardiograph is available to anyone; the interpretation of the tracing is the limiting factor and the greatest source of error. To interpret the records properly requires electrocardiographic knowledge and mature judgment, still a limitation of many clinicians. However, with ever-increasing effort, more and more physicians are learning to interpret the electrocardiogram. There is a need to continue to educate clinicians in this regard. A new shiny electrocardio-

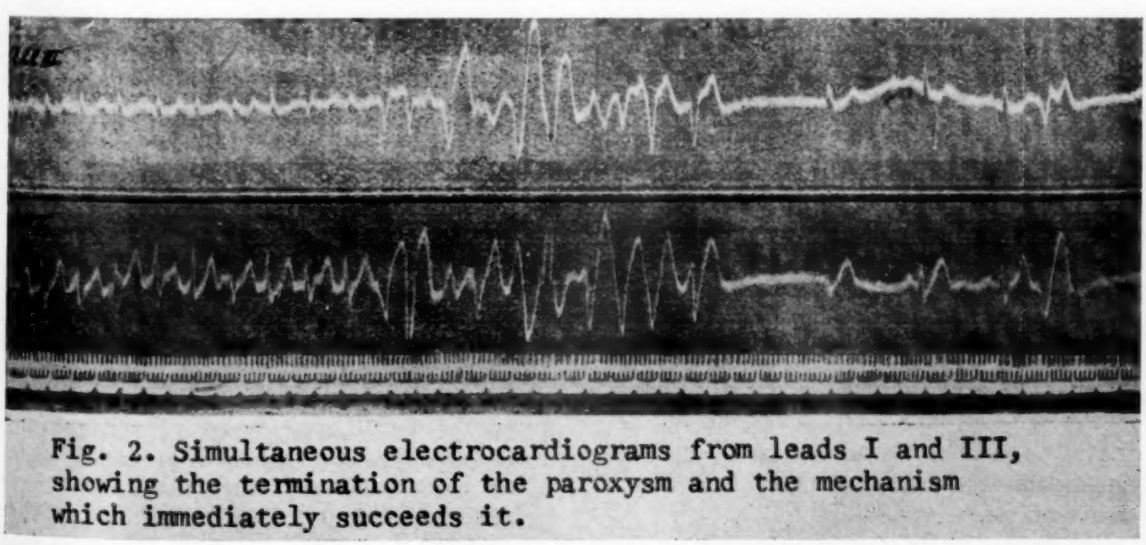


Fig. 2. Simultaneous electrocardiograms from leads I and III, showing the termination of the paroxysm and the mechanism which immediately succeeds it.

Fig. *17.* The first recorded electrocardiogram of ventricular fibrillation in man without death. (Reprinted from Hoffman: Heart 3:213, 1912.)

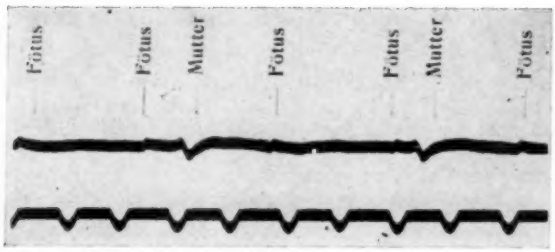


Fig. *18*. First recording of the electrocardiogram of the mother and fetus. (Reprinted from Cremer: München. med. Wchnschr. 53:811, 1906.)

graph or fine recording do not constitute good electrocardiography. Clinical electrocardiography can be no better than the man interpreting the tracing. Although known to many, this principle is too often forgotten and the patient suffers. It is not electrocardiography that is to be criticized but those who practice it. In the hands of the trained interpreter the electrocardiogram is a wonderful clinical tool; in the hands of the untrained, a dangerous weapon.

As with new drugs, so it is with new developments in electrocardiography, the most critical clinician succumbs to errors and difficulties which are detrimental both to the patient's health and his finances. Careful, methodical training in electrocardiography is needed and must be disseminated to all areas of the world to supplement the clinical study of the patient, but never to replace it. As with Einthoven, Lewis, Wilson, and others of the past, the leaders in clinical electrocardiography today consider the electrocardiograph as merely a tool which should be properly integrated in the over-all study of the patient.

Einthoven was on a lecture tour in Boston when he learned that he had been awarded the Nobel prize in medicine. Before he had received official notification, he was told of the newspaper announcement. He wondered whether this could be just an American joke, or a misprint in the *Boston Globe*, but when he learned that the announcement was a Reuters' news release, he was then certain of the data and, of course, delighted.

To illustrate the modest and self-critical personality of Einthoven it is only necessary to cite two experiences that he had with the clinical applications of his galvanometer. Johann T. Peters, a practicing internist of Amsterdam, told me several years ago that he once had a wealthy Dutch patient who returned from Java to consult him about his heart. During the course of study, Dr. Peters suggested that he go to Leiden to have an electrocardiogram recorded with Einthoven's new electrocardiograph. Peters, then a young man and a great admirer of Einthoven, recognized the importance of the instrument. Peters advised his patient to be sure to give Einthoven 100 guilders for his services. The patient visited Einthoven's laboratory, indicated the purpose of his visit, and had a recording made which was later mailed to Peters. When the patient offered to pay, Einthoven replied that he could not accept the money because he did not see how the electrocardiogram could be of any real service to him. The patient insisted and Einthoven again refused, indicating that acceptance of the money would not be honest or just. How-

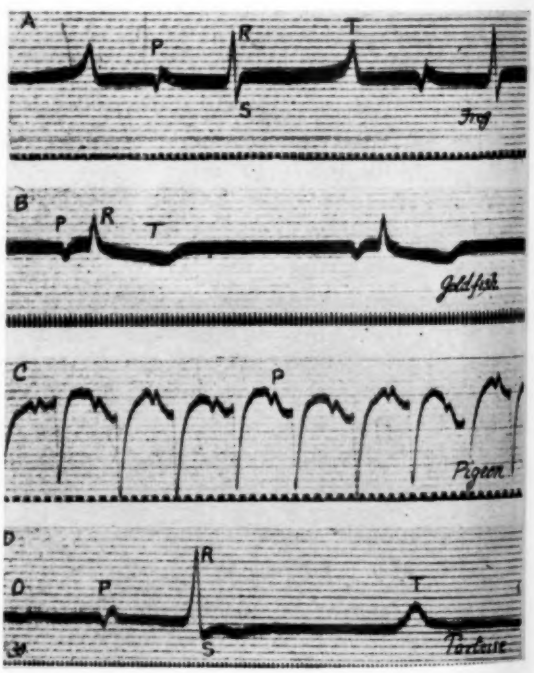


Fig. *19*. Electrocardiograms from various animals, recorded prior to 1915. Taken by leading off from the limbs with the heart unexposed. Electrocardiographic studies in animals were already beginning to have considerable influence upon the understanding of the human electrocardiogram. (Reprinted from T. Lewis: *Clinical Electrocardiography*, London, 1913, Shaw & Sons, Ltd.)

ever, the patient, loyal to Peters, thanked Einthoven, gathered his hat and coat and walked out, leaving 100 guilders on a table as he left the laboratory.

Samuel Levine, of Boston, tells of an interesting experience which occurred when Einthoven was lecturing in Boston at the time at which he learned of his Nobel award. As Einthoven and Levine were standing in a hallway at the Peter Bent Brigham Hospital discussing a problem, a technician emerged from the laboratory with a wet electrocardiogram in her hand, approached Levine and interrupted the conversation, saying, "Sorry to interrupt you, Dr. Levine, but this electrocardiogram shows that your patient has a fresh infarct. Should I notify the resident?" Levine said, "Yes." The technician left in a hurry, and Einthoven, astonished, asked, "Dr. Levine, you mean the technician was able to recognize myocardial infarction from the electrocardiogram and without the assistance of a trained cardiologist?" Levine assured him that this was correct.

Little did Einthoven realize the extent and influence his electrocardiograph was then having on clinical medicine. With the simplicity of use and interpretation of the tracing, even lay technicians were already becoming expert. One can only conjecture what his reactions would be today if he were to see the clinical applications of his instrument. Many patients today insist on an electrocardiogram for a thorough cardiac evaluation. Patients, in the United States at least, speak of T-wave changes and inquire about such changes. The "cardiograph" is a household word.

Anyone who reviews the history of electrocardiography is impressed with the fact that Einthoven was a great man, a simple, humble person who was so modest and self-critical that he was astonished by the accomplishments of his instrument and work. He was fortunate to observe personally the development of many fine things during his lifetime. Little did he realize that that was only the beginning.

In closing, may I express my appreciation and thanks to all of you of Leiden and Holland for this opportunity to discuss briefly the developments in clinical electrocardiography since Einthoven's report in 1903. To participate in this event in recognition of Einthoven is one of the greatest honors and opportunities of my lifetime. May medicine and science continue to flourish in Holland and the world for the health and happiness of mankind.

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Developments in phonocardiography

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It has been felt that this symposium, which aims at a survey of the present status of those fields in physiology and cardiology that were opened up by Einthoven, should also include a brief account of phonocardiography. In fact, although Einthoven's contributions to phonocardiography are not so important as those to electrocardiography, they are still of outstanding value. His first and probably greatest achievement was to register the heart sounds by means of the capillary electrometer, thereby making analysis possible for the first time (Einthoven and Geluk, 1894).[1] The carotid pulse and the apex beat were recorded simultaneously and served as reference tracings. It was pointed out that if one used a closed system for registration of heart sounds at the apex, only a cardiogram (apex-beat tracing) would be obtained, and that a small air leak had to be added in order to abolish the predominant vibrations of low frequency and to free the way for the study of the heart sounds. It was further stated that the heart sounds were not sounds in the physical sense but complex vibrations, that is, murmurs. The systole was divided into two parts, the period of building up of tension and the ejection period. Although this idea was not original (Einthoven referred to earlier observations of a different, that is, hemodynamic, nature by Hürthle and by Frédéricq), and although the criterion for this division, namely, the time lag between the appearance of the first sound at the apex and of that at the aortic orifice, does not seem appropriate, yet this notion was a very important one. In the same publication the phonocardiogram of an experimentally produced aortic insufficiency was shown.

In 1906, when optico-mechanical methods for pulse recording, such as Otto Frank's, had already been introduced, Einthoven improved his registration technique by using the string galvanometer. At first, one string galvanometer was available, by which either a single phonocardiogram ("cardiophonogram" as Einthoven used to call it)[2,3] or the superposition of a phonocardiogram and an electrocardiogram in one tracing (Fahr[4]) could be recorded. Obviously, the value of such a superimposed electrocardiogram as a reference tracing was slight, and one wonders why Einthoven, who had been familiar for a long time with the registration of arterial and venous pulse curves, did not continue to use them as reference tracings. It must be inferred that he did not think this point of great importance; otherwise he would certainly have found ways of improving his pulse records. As it was, they did not show many details and were somewhat less satisfactory, as far as the venous curve is concerned, than were Gibson's, of the same period. Both men (Gibson[5] and Einthoven[6]) discovered independently and at the same time the third

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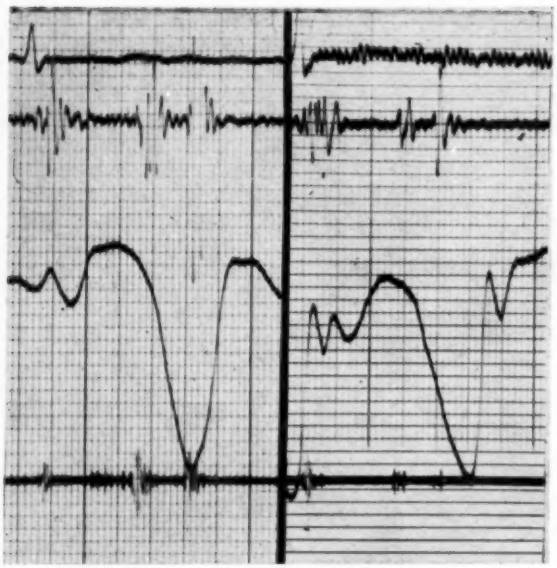

Fig. *1.* Constrictive pericarditis with third heart sounds. Male, born 1891. *Upper row:* Electrocardiogram. *Second row:* Low-frequency phonocardiogram (35 c.p.s.). *Third row:* Venous curve. *Fourth row:* Intermediate frequency phonocardiogram (140 c.p.s.). *Left:* Phonocardiogram taken at left sternal border; third heart sound coincides with bottom of the diastolic depression in the venous curve (i.e., end of the rapid filling period in the right ventricle). *Right:* Phonocardiogram taken at apex; third heart sound occurs definitely earlier, i.e., on the descending limb of the diastolic depression, thereby indicating its left-sided origin.

heart sound as a normal, although inconstant, phenomenon—Gibson by means of auscultation, Einthoven from his phonocardiogram. But both of them were led astray in their interpretation by imperfect recording of the time relations between heart sounds and pulse curves. Gibson attributed the third heart sound to closure of the atrioventricular valves, supposing it to be simultaneous with the b wave (in accordance with Hirschfelder,[7] now called h wave) in the jugular venous tracing. Einthoven, on the other hand, could not find this b wave in his curves and thought that the third heart sound was due to after-vibrations of the aortic valves.

Battaerd,[8,9] one of Einthoven's collaborators, published records obtained with two string galvanometers, showing simultaneously either two different phonocardiograms, for instance, taken at the apex and at the aortic orifice, or a phonocardiogram and an electrocardiogram. Photographic enlargement of these tracings and careful analysis of the vibrations revealed the presence of high frequencies up to 1,000 cycles per second. The amplitude of these vibrations, however, was very small and now appears insufficient. It was further shown that, in the phonocardiogram taken at the apex, initial vibrations of low frequency could be detected occurring only a few thousandths of a second after the onset of the QRS complex, followed 0.06 second later by vibrations of higher frequency, the first thought to be due to muscular contraction and the latter to valvular movement. The value of the electrocardiogram as a reference tracing, especially in irregularities of the heart, was stressed, and the differences as well as the similarities of auscultation and phonocardiography were discussed. Rightly it was pointed out that, whereas the ear shows a widely different response to varying frequency, it is, on the other hand, capable of ignoring extraneous disturbances which the instrument faithfully records. Battaerd's opinion (doubtless also that of his teacher, Einthoven) was that phonocardiography should supplement, not supplant, auscultation.

It has been stated already that Einthoven, who laid the foundation stones for

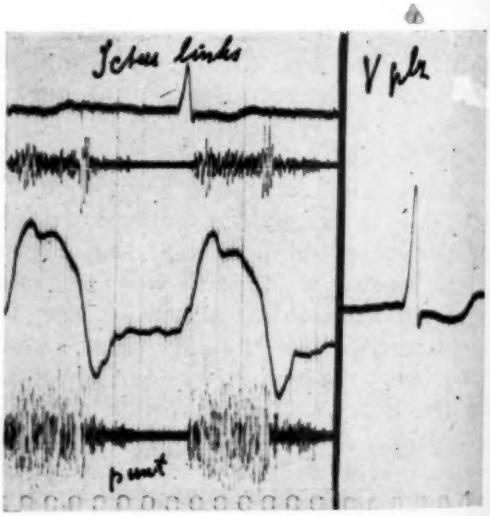

Fig. *2.* Mitral stenosis and insufficiency. Female, born 1909. *Left:* Apex-beat tracing taken with the patient lying on her left side, and phonocardiogram. Distinct delineation of first (rapid) filling phase in the diastolic part. Phonocardiogram shows pansystolic murmur and short diastolic murmur starting after the opening snap. The latter coincides with the bottom of the apex-beat tracing (beginning of diastolic filling of the left ventricle). *Right:* Precordial ECG taken at apex.

both electrocardiography and phonocardiography, was more successful in the development of the former than of the latter. Presumably, this was due to the fact that phonocardiography is highly dependent on clinical and pathologic findings for its interpretation. It follows that the limitation of diagnostic facilities and knowledge of those years must have been a greater obstacle in the pathway of phonocardiography than of electrocardiography. Furthermore, there was an unfortunate loosening of the psychologic ties between the clinic and the laboratory in spite of the well-functioning physical connection between the two, described in Einthoven's article on the telecardiogram. After the work resulting in Battaerd's thesis, published in 1913, Einthoven did not add much to the field of phonocardiography, except a technical improvement consisting in the construction of the string phonograph, which he described with his pupil Hoogerwerf in 1924.[10] No further use of this instrument was made, however, during the few remaining years of Einthoven's life.

Time does not permit us to follow the further development of phonocardiography, but we must look at how the subject stands today. The recording technique has been improved in many ways, and the necessity of using filters (in the plural sense) has been established. Apart from spectral phonocardiography, which, interesting as it

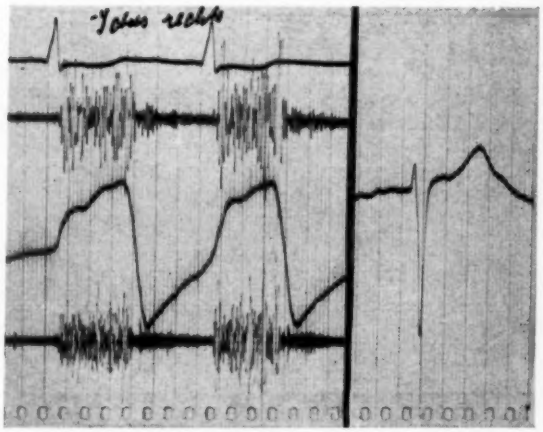

Fig. *3*. Same patient as in Fig. 2. *Left:* Apex-beat tracing taken with the patient lying on her back. No clear distinction between rapid and slow filling phases. Opening snap precedes the point indicating beginning of diastolic filling (in this case, of the right ventricle). *Right:* Precordial ECG taken at apex.

is, has yet to prove its clinical value, frequency bands of varying width and definition are being used. It would seem that efforts directed toward standardization, such as were recently undertaken in this country by a committee of the Netherlands National Health Research Council T.N.O., may be useful. It should be possible to establish an international agreement about the requirements for clinical phonocardiography which could yield comparable records from different hospitals. Obviously,

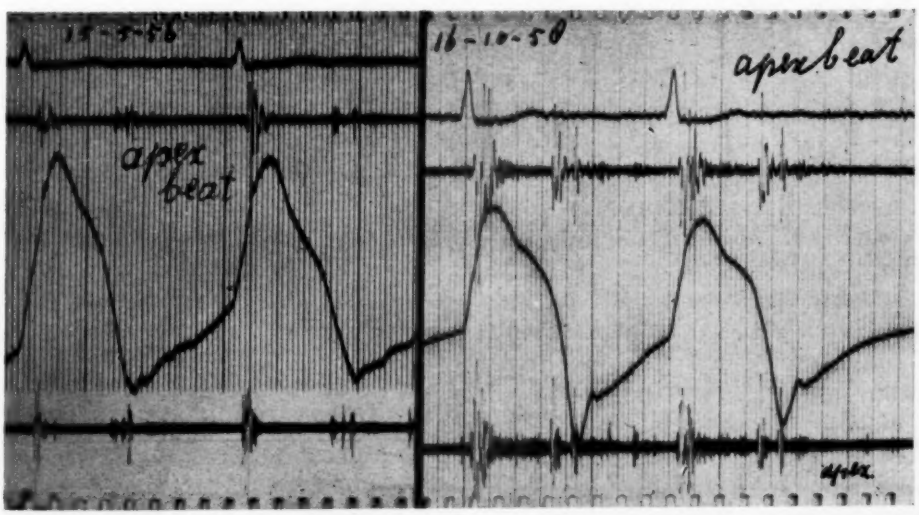

Fig. *4*. Mitral stenosis. Female, born 1913. See text. *Left:* Before operation. *Right:* After commissurotomy.

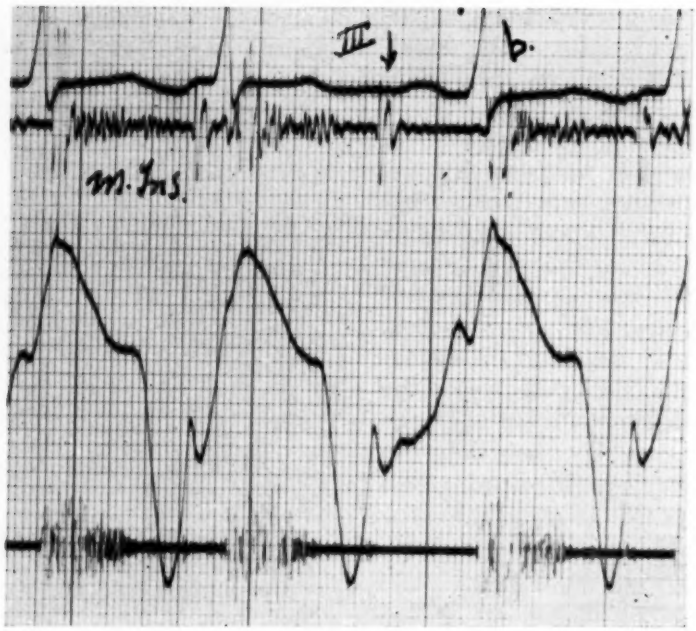

Fig. 5. Mitral insufficiency. Male, born 1909. See text.

for research purposes there will always be the need of other than routine methods, for example, a study of the very high frequencies. At the present time, however, some cardiologists still have to be convinced that the aim of phonocardiography should not be to imitate auscultation nor to endanger it as a rival, but to give supplementary information, as was already clear to Einthoven.

Many advances have been made in the last thirty years, but most of them were foreshadowed by subtle auscultatory observations, especially from the French school of Potain, Vaquez and Laubry. (Parenthetically, at the same time these clinicians acquired a large experience in recording cardiograms and pulse curves, a field which unfortunately has lately been neglected, even in Paris, as appeared from a recent visit.) The six heart sounds (including the systolic ejection sound, the opening snap of the atrioventricular valves, and the four classic sounds), to which could be added the mid-systolic click, the summation gallop sound, and the sound of transient closure of the atrioventricular valves, have been identified, and the origin of murmurs has been established to a large extent. Some of these, although clinically important, have been recognized as representative of functional, that is, relative, nonorganic, stenosis. To cite an example: the relative pulmonic and tricuspid stenoses in atrial septal defect are responsible for the only (and diagnostic) auscultatory signs in this condition, apart from the reduplicated second sound, which is probably due to the concomitant bundle branch block. On the other hand, all protosystolic murmurs belong to the same type, and, in fact, as far as this murmur is concerned, phonocardiographic differentiation between a slight or moderate pulmonary stenosis, an atrial septal defect, and a functional murmur due to increased cardiac output, as in anemia, may be very difficult, if at all possible. So we are led back to the old concept of relative stenosis (and, of course, insufficiency) of valves.

However, in our opinion, the chief gain is that lately we have learned to look at the phonocardiogram from a hemodynamic point of view, and it has become clear that the phonocardiogram may be used as a reliable guide in hemodynamic interpretation. This is only true on one condition, however. One should not be satisfied with the electrocardiogram as a reference tracing for timing the phonocardiographic events; all available information should be used. This means that simultaneous recording of various pulsations, such as those of the jugular vein, the carotid, subclavian

and femoral arteries, of the heart itself at the apex and elsewhere in the precordial region, is indispensable. If necessary, further information can be obtained from simultaneous pressure tracings obtained by heart catheterization and (or) electrokymograms of the heart and the great vessels.

Another old but clinically very important notion has come back to us by way of modern phonocardiography. Obvious as it may be, its implications have not been generally recognized as yet. We are referring to the independence (limited, of course, but hemodynamically important) of the right and left heart. Consequently, a certain extent of asynchronism is possible and does occur even under normal circumstances. In pathologic conditions the asynchronism may be greatly increased, and the normal sequence may be reversed. Splitting of the second

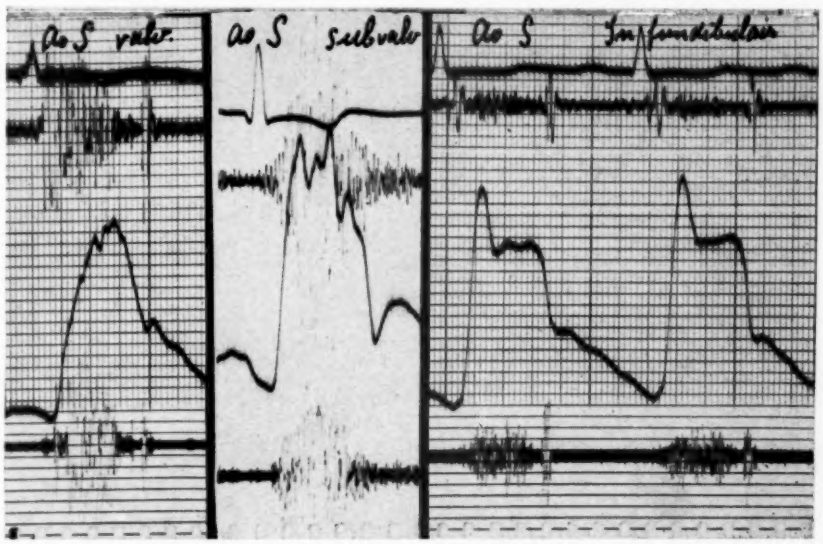

Fig. 6. Aortic stenosis. *Left:* Valvular type. Female, born 1909. Phonocardiogram shows ejection sound, diamond-shaped systolic murmur and late aortic part of the second sound (reversed splitting). Carotid pulse. See text. *Center:* Subvalvular type. Male, born 1942. See text. Diamond-shaped systolic murmur is followed by protodiastolic murmur. *Right:* Infundibular type. Female, born 1907. See text.

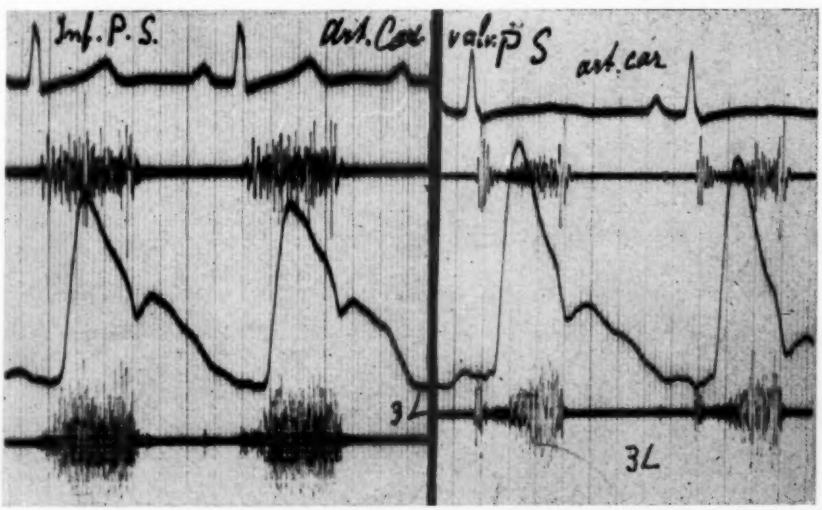

Fig. 7. Pulmonic stenosis. See text. *Left:* Infundibular type. Female, born 1946. *Right:* Valvular type. Male, born 1942.

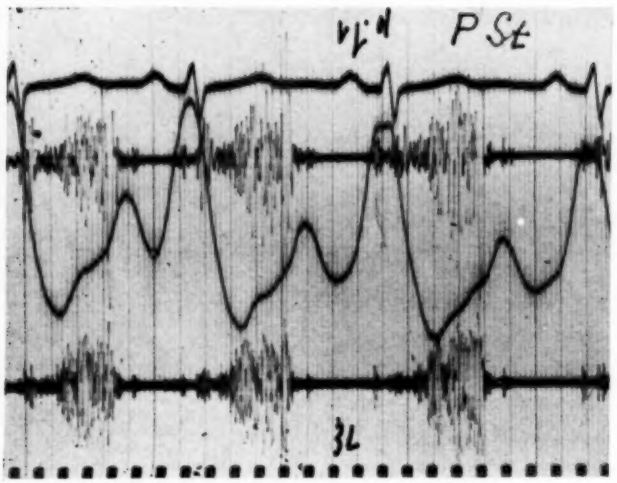

Fig. *8*. Valvular pulmonic stenosis. Female, born 1936. Venous curve with phonocardiogram. See text.

sound was already explained by Potain on the basis of nonsimultaneous closure of the aortic and pulmonary valves. In the same way we have now come to accept the existence of separate third and fourth sounds from both sides of the heart, although actual reduplication is rare. Sometimes, however, a third sound from both sides of the heart may be found (Fig. 1), and it is highly probable that the so-called fifth sound is no other than a right-sided third sound. Furthermore, the occurrence of a right-sided opening snap was demonstrated by Leatham in cases of atrial septal defect.

It should be mentioned here that the apex beat, which is a very rich source of information in clinical practice, especially in relation to the diastolic filling of the heart and the impact of atrial contraction, may also constitute a problem by having a left-sided or right-sided (or sometimes a two-sided) origin. The finding of a right-sided apex beat is in itself an important clinical sign, for example, as an indication of the true nature of a systolic apical murmur in the case of a severe mitral stenosis without distinct diastolic rumble, but with pulmonary hypertension and relative tricuspid insufficiency. The same finding may also aid in differentiating atrial septal defect of the ventral and dorsal (so-called primum and secundum) types.

How does one recognize the right-sided apex beat? Partly by its rounded diastolic contour and by comparison with the jugular venous tracing, but better still by the aspect of the electrocardiogram taken exactly at the place of the apex beat, provided that this electrocardiogram shows a typical pattern (qR or qRs for the left and rS for the right side), which is unfortunately not always the case (Figs. 2 and 3). Our experience so far, both in connection with the phonocardiographic tracings and with the epicardial leads obtained during operation, seems to indicate that this is a reliable sign.

In closing, we wish to make it clear that the usefulness of the pulsation tracings is not limited to the interpretation of the phonocardiogram, but that their pattern in itself gives extremely valuable indications pertaining both to the diagnosis and to the severity of heart disease. In fact, the degree of mitral stenosis, pulmonary stenosis, and aortic stenosis, to mention a few operable conditions, can be fairly well assessed from the phonocardiogram in conjunction with the pulsation curves—so much so that the need for right-sided or left-sided heart catheterization is thereby greatly reduced for practical purposes. The same applies to the localization of aortic or pulmonary stenosis (valvular or infundibular with the subvalvular region between them). Valuable information in this respect may be obtained, of course, with selective angiocardiography, but as long as this cannot always be expected to

be quite innocuous, especially in the left heart, the harmless and simple procedure of taking a phonocardiogram with pulsation curves, which in most cases is sufficient to localize and to estimate the stenosis, should be the first and often even the final approach.

A few examples may serve to illustrate these statements.

The first (Fig. 4) concerns the pattern of the apex-beat tracing, in particular of the initial rapid phase of diastolic filling in mitral stenosis before and after operation in the same patient. In both cases the opening snap is clearly visible and is seen to coincide with the beginning of diastolic filling. Before operation, however, the rapid initial phase is very small; it is virtually normal after commissurotomy. The next tracing (Fig. 5) shows a further exaggeration of the rapid filling phase and the occurrence of a sharp peak at the end of it in mitral insufficiency. There is no opening snap, but a third heart sound is present, which coincides with the peak.

Next, Fig. 6 shows the carotid pulse contour and the phonocardiogram in the three different localizations of aortic stenosis. In all three the ejection time is lengthened and the aortic part of the second sound is late when it is visible. In the valvular type the ascent of the carotid pulse is slow and leads to a plateau with coarse vibrations; there is also an ejection sound, except in some cases which show extensive calcification of the valves. The infundibular type, in which case the stenosis is well below the valves in the muscular part of the ventricle, shows a steep rise of the carotid pulse, followed by an early descent to a horizontal plateau without vibrations. There is no ejection sound. Finally, the immediately subvalvular variety shows a carotid pulse contour very similar to the valvular type, although the ascending part is steeper. So far no ejection sound has been found in these cases in our material.

The last example concerns valvular and infundibular pulmonary stenosis. The difference in the systolic murmur is obvious (Fig. 7): an almost equal amplitude throughout the whole of systole in the infundibular type, with a frankly crescendo murmur in the valvular type of marked or severe stenosis. Both murmurs exceed the point of the carotid incisure, indicating lengthening of right-sided ejection time. The venous curve in a case of severe pulmonary stenosis (Fig. 8) shows exaggerated A waves, and the phonocardiogram a fourth sound with a slight presystolic murmur, all due to increased right atrial pressure.

It is possible to give other examples, but we hope that those which have been presented will suffice to explain the present growing interest in phonocardiography.

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A day's discussion on electrocardiography

Summary of final remarks by Dr. G. Giraud*

Dr. Giraud, having been asked to speak, and at the same time to summarize the papers given during the afternoon and to direct the discussion, began by offering his thanks to the School of Medicine in Leiden and to Professor Snellen for the honor which they had bestowed upon him.

The afternoon had been devoted to three papers, all of unusual interest but differing much in nature. The first had been given by Dr. H. C. Burger, the second by Dr. G. E. Burch, and the third by Dr. H. A. Snellen.

Dr. Burger's paper. In his paper on heart-vector and leads, Dr. Burger expounded his personal views with renewed vigor. He criticized the present method of vectorgraphic delineation of the heart's activity and condemned the old methods which are geometrical and intuitive. He has criticized the fallacious argument based on the equilateral triangle and also that related to the regular tetrahedron of Wilson. He has given us a rational foundation of electrocardiography and of vectorcardiography regarded as functions of linear equations. Furthermore, he attacks the systems developed by Frank, Schmitt, and McFee, which are based on the hypothesis of a homogeneous material, and, in contrast, has expounded his own theories based on consideration of a material with heterogeneous characteristics.

At the present time, Schmitt finds it necessary to use fourteen electrodes, whereas McFee employs nine and Burger keeps five, but Burger has suggested that, if there is still some possibility of standardization, the chances thereof are not great and perhaps they are not practicable.

The speaker remarked that all those present must have been aware of the warmth with which Dr. Burger developed his argument, but since Professor Rijlant, of Brussels, was present, it was highly desirable that he should be asked to give his views. Nothing could be more profitable than debate between these two eminent physiologists, because each is a master in the field of modern methods of vectorcardiography. In consequence, Professor Rijlant was then asked to speak.

Discussion by Prof. Dr. P. Rijlant. Burger's attempt to establish a statistical correlation between vectorcardiographic methods as they are used today emphasizes the over-all usefulness of the vectorcardiographic approach. They also call our attention to the important discrepancies.

These methods are adequate for diagnosis and perhaps also for clinical research. They are quite simple and do not call for extensive or intricate equipment.

On the other hand, research in physiologic or medical laboratories has a need for more accurate and less empirical methods. These methods should be adequate not only for human vectorcardiography but also for experimental research on the exposed or isolated heart of laboratory animals.

The easiest and safest approach is the integration of all the information available at the surface of the body or of the exposed heart, to build up a dipole equivalent of

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the electrical generators inside the heart.

The whole of the body surface is explored by seventy-two regularly spaced electrodes, either in man or the intact animal. For the isolated or exposed heart, twenty regularly spaced electrodes enclose the heart in a regular dodecahedron.

To provide for a precise location of the electrodes and also to speed up the procedure, the electrodes are permanently affixed on an elastic jacket or on an elastic network. In man or intact animal the skin is rubbed with a conducting paste.

The electrodes feed current into a three-dimensional conducting, homogeneous medium of non-Euclidean geometry. This conducting medium is built up by several thousands of identical resistors; it is symmetrical in respect to three orthogonal planes. Distribution of current inside the network, at a safe distance from the input electrodes, is such that direct measurement of the orthogonal axes of the dipole moments can be attempted. Control experiments on models have shown that the accuracy is better than 95 per cent.

Simultaneous recording of the three dipole moments provides for the vertical, transverse, and anteroposterior vectorelectrocardiograms as opposed to the commonly used scalar electrocardiogram and the frontal, sagittal, and horizontal vectorcardiograms.

A precise analysis of either the QRS, the T, or also the S-T components is made possible by the use of resolvers that provide for the rotation in space of the electrical axes. This rotation has shown that in at least 95 per cent of several thousand normal young individuals the QRS loop lies in a simple plane. The T wave is not located in the same plane. There is no rotation of the T vector in normal man, dog, or rabbit. The so-called T loop is due to interference with the S-T component. This S-T component is present in at least 30 per cent of normal individuals; its size is about 15 to 40 per cent of the size of the T component. It is always oriented at right angles to T, which makes for the T loop. The end of the S-T component is always four hundredths of a second before the end of the T wave.

Although the clinician does not feel, for the time being, the need of more accurate vectorcardiographic methods, experimental research is dependent on a more precise knowledge and on methods that provide for adequate means of measurement of either physiologic or pathologic variations of the global electrogenesis of the heart.

To increase the accuracy of the methods employed, recording on magnetic tape is used as a method for storing the information, and these records can be analyzed at leisure at a later stage. This storing of information should be considered in the near future as a routine method to shorten the time needed to collect the available information, the extensive analysis being postponed till a more suitable moment. Perhaps this will provide for a sharing of the burden by the clinician who collects the information and the physicist who analyzes the information.

Dr. Burch's paper. In his paper, Dr. Burch gave a most dramatic picture of the clinical developments in electrocardiography since the time of Einthoven. Dr. Giraud suggested that it was highly desirable that all present should have the text of this exposition, which had up to that time never been made with such clarity and completeness.

Dr. Giraud also thanked and congratulated Dr. Burch for his remarks, and pointed out that he had not gone further than the introduction of external precordial methods in using the leads. He expressed the hope that a new chapter had been opened which may be added to those already described in such a masterly manner. He had in mind electrocardiography with leads taken from the cavities of the heart and also the use of similar methods with leads taken directly from the outer surface of the heart in man, this procedure now being possible because of the advances made in thoracic surgery. Epicardial readings, as used in animal experiments, have provided most valuable information. This method of investigation has made it possible to study the behavior of certain parts of the auricles which previously had been out of reach. In this connection, the experiments carried out by Paul Puech were of interest.

Endocardial electrocardiography, as introduced into France, by Lenègre, and elaborated by the school of Montpellier,

has to its credit much new evidence. The procedure has been known for some years and is in present use; it has thrown much light on certain areas about which we knew little before. A true endocardial and direct method has been made possible in the right heart, and sometimes in the left heart in the presence of septal defects. Alternatively, the behavior in the latter has been examined by retrograde methods through the arterial system. It has been possible to investigate all parts of the various heart cavities and to record either the sum total of the electrical changes occurring in the heart as a whole or those which occur at the point at which the electrode is resting and at which the greatest electronegative deflection is most marked. Dr. Giraud remarked that this was not the occasion for describing all the new information gained by this new procedure, but he could point out that during fibrillation of the auricle there were many foci of activity in sundry parts of that cavity which exhibited variations in frequency. Furthermore, these methods had thrown new light on the Wolff-Parkinson-White syndrome. We now know more about the electrical changes originating in the coronary sinus, of the changes occurring in Tawara's node, and of those in the main part of the bundle of His. Further information has also been obtained of the myoneural roots in the neighborhood of the coronary sinus which are found before regrouping in Tawara's node. The waves of activity in these various parts have now been elucidated with great exactness, this being a new development in 1960. Further studies are being carried out in stages; not a term passes which does not give us new information. All this has been possible because of the magnificent work of Einthoven.

Dr. Snellen's paper. The third paper was that read by Professor Snellen, who dealt with phonocardiography. It was at this moment of Dr. Giraud's address that Dr. Snellen interrupted to point out that the time allotted for the papers in the afternoon had passed and that the moment had come to receive the family of Willem Einthoven, this being the real purpose of the commemorative meeting.

However, the speaker asked Professor Snellen's permission to make a few remarks on the very fine paper which Dr. Snellen had submitted.

Dr. Giraud pointed out that in the field of phonocardiography the Professor was like an apostle who could read in the tracings all sorts of things which others had failed to observe. This could only be possible by a most perfect technique and in the light of much experience and great powers of observation. One has to admit that Dr. Snellen can find evidence from his tracings of a most exact and subtle nature, which no other person has yet found possible.

He has demonstrated the parallelism which may be shown between direct intracardiac catheterization and the information obtained by graphic methods. He has defended the information obtained mechanically which tends today to be so easily forgotten, but which in the time of Marey was so widely and so informatively used.

Dr. Snellen has even been able to describe certain indications in important cases whereby he can dispense with the information given by catheterization in considering certain operative procedures. Speaking for himself, he felt that in many of his opinions he was right, although it was well known that a decision to operate could rarely be justified on one point of evidence alone. All possible information and all information gained by metrical methods should be summarized and related to the clinical findings. One could not be too well informed, and in this respect the path shown by Professor Snellen has led to a rich harvest, both now and for the future. He would, nevertheless, point out that the cardiologist and also the general physician found it necessary to synthesize all the information about the patient which could be obtained.

At this point, some members of Einthoven's family, including his two daughters and his grandson, entered the meeting, together with the official representatives of Leiden University, to hear the reading of the two commemoration papers of Einthoven's former assistants: de Waart and Regnier.

Einthoven Commemoration

A. de Waart, M.D.

The Hague, Netherlands

During the years I worked with Einthoven, i.e., 1909-1913, Leiden was a very quiet little town. There were hardly any automobiles; at any rate, none of the professors had an automobile. A horse-tram connected the station with the Hogewoerd, passing the Breestraat with moderate speed. Along the Rijnsburgerweg, then a narrow road allowing a beautiful view over the meadows as far as the old castle of Poelgeest, there was a primitive steam-tram. I lived in that Rijnsburgerweg just across the toll, which at that time separated Leiden from Oegstgeest. This was the favorite road Einthoven chose in the evenings for his stroll. Since the time of his student days at Utrecht, he had liked very much to walk and to ride on bicycle. Going to his laboratory, he always crossed Leiden on bicycle, and in case of rain was protected by a very special coat, the kind which was also worn by the celebrated pianist Pembauer. On the last Saturday of each month, Einthoven could be seen at the station, wearing a top hat, on his way to the monthly meetings of the Academy of Sciences. He lived at that time in the Oegstgeesterlaan, now called Boerhaavelaan. Occasionally, we walked together and sometimes we discussed the textbook of electrocardiography which he was writing, and the difficulties arising from the fact that new discoveries continuously loomed up, which he liked to include in this work. I think this book never appeared as such, but later on became the basis for his posthumous monograph, "Die Aktionsströme des Herzens," in Bethe's Handbuch, 1928, which remains a masterpiece and still ought to be read by anyone who concerns himself with this branch of science.

I was asked to discuss Einthoven's personality, without laying too much stress on his work. This is rather difficult. Work and personality cannot be separated entirely, because the personality leaves its impress on the work and shows itself in the work.

Moreover, to discuss his personality by itself is not at all in Einthoven's line. He did not attach much value or importance to his own personality. What he valued was objective and honest science, and what he admired was Nature.

What we call character seems partly hereditary and partly acquired. The upbuilding of character occurs partly at home, but also in a good school and in a good university, under the influence of good masters. Einthoven's scientific mind developed under the influence of Donders. He often spoke to us of Donders, but also of other classic figures, such as Helmholtz, du Bois Reymond, Johannes Müller, and I am convinced that the lives of those men inspired him and helped him to develop his own personality.

In Einthoven's work we notice again and again how he persevered. He could point out to a new assistant on his very first workday the necessity of persevering.

Address given on June 25, 1960, at Leiden University, by Dr. de Waart, Professor Emeritus of Physiology, in commemoration of the centenary of the birth of Willem Einthoven (1860-1927).

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He used to say, "Perhaps you read books about scientists making a new discovery each day. These books don't tell the truth. Often you have to spend several months only on the improvement of an arc-lamp, or another number of months only on locating a leakage in a vacuum-pump."

As a true investigator, Einthoven thought as much of what we are ignorant of as he did of what already had been made clear. His chief interest was always in the territory which had not yet been traversed. He was a real explorer and pioneer. He sought the facts of life in adventures beyond the frontiers. He addressed Nature herself and penetrated to the center of her mysteries. His ingenious and inventive imagination served to indicate where and what the problems were, and to suggest and find methods for solving them. And his perseverance brought him to the solution. In this he resembled in many respects Helmholtz, who describes the invention of the ophthalmoscope as follows: "It was first so difficult, that I doubt if I should have persevered unless I had felt that I must succeed."

Again and again Einthoven showed this perseverance in work and thought. Experimenting with the capillary electrometer, he studied this instrument for not less than 7 years (1893-1900), meanwhile also persevering in inventing and constructing his string galvanometer, which he described in 1901, publishing the first human electrocardiogram recorded by it in 1902. In 1903, he states: "Ich habe schlieszlich ein Instrument herstellen lassen, das . . . im Stande ist das menschliche Elektrokardiogramm unmittelbar in nahezu richtigen Verhältnissen zu schreiben." This simple word "schlieszlich" reflects perseverance: working hard daily for many years. And still he was not satisfied. His most perfect instrument came in 1926, and, working in cooperation with his son, he developed in 1923 the vacuum galvanometer, which was also used in the wireless of those days. But this latter instrument he had already planned in his papers 19 years before, in 1904, so that here again we see his perseverance.

We meet this mental trait again in the development of the triangle scheme. As early as 1896 and 1900 (capillary electrometer work with de Lint), and in 1908 (string galvanometer work with Vaandrager), be discussed the possibility of determining from the electrocardiogram "die Lage des Herzens oder der Herzachse," and, persevering, he announced the triangle scheme in his Chelsea lecture of 1912.

More examples of his great perseverance would be easy to find. Suffice it to say that he was not content when there was still reason for doubt; he did not rest before he hit the mark.

Einthoven's sole motivation in his work was to discover the truth in many fields of physiology. Moreover, he lived to see his services to science applied with great success in the clinics. He promoted this success himself by recording (tele)cardiograms and phonograms of patients; for many years his laboratory afforded the sole place in the world where this could be done. He was always ready to assist his clinical colleagues and general practitioners and their patients, even if he had to interrupt other activities.

I told you already that Einthoven did not attach special value to his own personality. Modesty was one of his principal traits. He remained as much as possible in the background. Even when he talked about his own work, he tried to conceal his own name. In his rectorial address of 1906, neither his name nor that of his laboratory can be found in the discussion of his fundamental researches on the electrocardiogram, the electroretinogram, the vagus-currents, and the heart sounds. He never allowed anything about himself to enter the newspapers. All jubilees were kept out of the press, and he was absent from Leiden on such occasions.

In 1925, it was made possible for me to visit a number of universities in the United States. Quite by chance I passed through many institutes and laboratories where Einthoven had been some months before. Everywhere it proved that he had created a feeling of friendship and intimacy by his broad-minded and genial personality. He had been involved in many scientific discussions, but, in his usual way, he always kept his own person in the background. For example, in Cleveland, differing with Wiggers concerning the identity of electrical and mechanical activities of heart

muscle, he pointed out that investigators should perhaps expend more energy in attempts to harmonize differences rather than to gather more and more experimental evidence in favor of a previous conclusion, and he said finally, "The truth is all that matters, what you or I may think is inconsequential."

During his stay in America, he was awarded the Nobel prize. Interviewed by journalists about his work, he said, "I cannot expose to you my own work, other people may do that if they like."

Having seen in Boston the work of Forbes, who combined the string galvanometer with radioamplification in nerve research, I asked, in the autumn of 1925, Einthoven's opinion about these experiments. His answer was, "This has also been done by others, but they got disappointed." Afterward I discovered that he himself had done it, but he never told me this personally.

Einthoven lived at that time in a kind of reconstructed farm on the banks of the Old Rhine. There he had a comfortable and quiet round study, which was a part of an old mill, surrounded on all sides by a balcony, permitting a nice view in all directions.

Besides his will to persevere and his modesty, we want to stress his honesty and idealism.

He always gave others the credit and honor they deserved.

In 1891, commemorating the late Isebree Moens, he states that the Leiden professorship was for the first time offered to that scientist rather than to himself. In 1885, in his paper on the vagus effects on bronchial musculature, he praises MacGillavry for his former researches on this subject. In 1895, describing his new method for correcting the tracings of the capillary electrometer, he calls the older method of Burch "eine vorzügliche Arbeit." In 1906, he states that the idea of connecting his laboratory to the hospital for the purpose of taking telecardiograms originated with Bosscha. In 1907, giving the first records of the third heart sound, he does not omit to praise the skill of Dr. Gibson, of Oxford, who was the first to hear this sound. In 1916, after proving that Gaskell's opinion about the electrical vagus effect on the heart was not valid, he remarks nevertheless, "Wir möchten an dieser Stelle betonen, dasz wir, obgleich Gaskell's Schluszfolgerungen bestreitend, seine Arbeit doch gern anerkennen. Es sei daran erinnert, dasz sie ausgeführt wurde in einer Zeit wo die elektrotechnischen Hilfsmittel weniger volkommen waren als heutzutage. Seine genaue Untersuchungen über den Bau und die Innervation des Schildkrötenherzens verdienen unsere Bewunderung, und es ist ihm zu verdanken, dasz die vorzüglichen Eigenschaften dieses Organs, die es besonders zum Gegenstand physiologischer Untersuchungen eignen, allgemein bekannt geworden sind."

And how often did Einthoven not value highly the work of Sir Thomas Lewis? Even when receiving the Nobel prize in Stockholm in 1925, he said in regard to Lewis, "Without his valuable contributions I doubt that I should have had the honor of appearing before you today."

Einthoven certainly also was an idealist.

Idealism has been a very pronounced attribute of great masters of medicine. It expresses itself in a strong desire to pursue ideal ends at the cost of the ordinary prizes of life: wealth, material power, and physical comfort. But not always have the motives of scientists been purely altruistic. Examples could be given, of a master who patented an antitoxin avowedly with the intention of gaining money for further research, but at the same time raising the cost of this antitoxin to the patients; or of another master who secured for himself a patent for his method of narcosis. But Helmholtz gave his ophthalmoscope freely to medicine, and Pasteur gave his great discoveries freely to the world. Einthoven never aimed at earning money by his work. He already fully described his string galvanometer in 1901. He gave it freely to medical and physical science in his paper of 1909, "Die Konstruktion des Saitengalvanometers." He freely helped trustworthy concerns to duplicate it. He gave every possible information to Williams, who built the first instrument in America and promoted development of electrocardiography in that country. He kept away only those people who, intent on the making of money, produced imperfect instruments, and thereby caused much

misunderstanding in science. Honest and scientific people always had free access to the laboratory.

Concentration on research requires peace of mind. If an investigator is married and has a family, their happiness and contentment are important to him. Einthoven himself has often testified that he had a happy family life, and we were all aware of it. Mrs. Einthoven greatly aided her husband to proceed in his academic work. Out of that happy and sound family atmosphere, also emerged the son Willem Frederik, who played a fundamental role in the birth of the vacuum galvanometer, and who later on gave to Java a brilliant institute of radiotelegraphy. We often met this son in the laboratory when he was just a young boy. He showed a remarkable interest and ability in mathematical, mechanical, and electrical problems, and followed in his father's footsteps, sometimes even preceding him. (He died as a prisoner of war in Tokyo, in 1945.)

The original work performed in the institute of physiology attracted many distinguished visitors, e.g., Madame Curie, Pavlov, Samoiloff, Waller, Westerlund, Jolly, Misslawski, Lewis. Sincere international contact and friendship existed.

Einthoven kept his laboratory active and pliable by never trying to build a permanent staff. Junior men and foreigners were encouraged by being given attractive work. As a rule, they had consecutive periods for research and for teaching in the practical exercises. The didactic lectures were given by Einthoven himself. But here also he proved his modesty. If a man of teaching experience asked to attend these lectures, Einthoven said, "Don't waste your time, it is not worth while, I make too many mistakes." The strain of intense mental effort never affected his kind attitude toward medical students. He could understand that students cannot absorb in two years all the knowledge that professors gain in a lifetime. He was very humane in his examinations, but always honest and not weak. In our historical museum a letter can still be found in which he reprimands in rather strong terms a man who did not live up to his expectations.

Scientific work with Einthoven was not at all one-sided. Since most of the experiments could not be carried out without an assistant, the members of the small staff worked, as a rule, in pairs, each acting as assistant to the other on alternate days. Consequently, they learned in many ways under Einthoven's guidance, and it was possible for nearly all not only to get practical experience in experimental and clinical electrocardiography and phonography, but also in electrophysiology of different nerves and muscles, and even in the x-ray technique of those days. We all developed our own photograms, taken on glass plates, and spent part of our life in the dark room. Handling the original and for some time the sole galvanometer with its at that time unsurpassed merits was not so difficult. Inserting a new string, however, was more complicated and was performed only in the presence of the professor. Yet the same string might last many years and be used in the most divergent investigations.

A century has passed now since Einthoven's birth. This centenary is not a cause for grief. It is a cause for rejoicing and thankfulness, remembering his great personality and contributions to science, to his university, and to international friendship.

The instruments with which, and the surroundings in which, we work today have changed immeasurably from what they were before; additional experiments will always be necessary to fill the gaps in our knowledge, but if we are to succeed, the spirit in which we work must remain the same as that in Einthoven's days. As in those days, we must realize that science is and has to be an international tree, bearing fruits for the well-being of mankind, uniting peoples and nations all over the world.

After Dr. de Waart's paper a short record adapted from a dictation by Einthoven on an Edison phonograph was heard. Its subject was the telecardiogram, i.e., the electrocardiogram made in Einthoven's laboratory of a patient who was in the University hospital at a distance of a mile. This text was ultimately published in Bethe's *Handbuch der Physiologie.*

In memory of Einthoven*

*M. Regnier, M.D.***
Brussels, Belgium

I must ask you to excuse the emotion which I feel in finding myself among you to commemorate the centenary of the birth of Willem Einthoven, and also for the deep feeling which moves me when I think of the honor that you have given me in asking me to speak. I will endeavor, as a representative of Einthoven's former foreign assistants, to express in modest terms our feeling for his splendid personality and for a man who was beloved because of his apparent severity, a man who was such a complete individual by reason of the exquisite balance of his outstanding scientific, human, and moral qualities.

Professor De Waart has drawn attention in a masterly manner to the greatness of Einthoven's character, the constancy of his life, and his ideals. He has described his modesty of spirit, his scrupulous respect for the work of others, his unselfishness of thought, charity of heart, and the general aim of his life. Without thinking of himself, Einthoven aimed at knowing and discovering truth in Nature through all living beings, so that all men might benefit from an increase in knowledge. To this end he promoted rigorous, scientific enquiry in many fields, but particularly in the field of physiology and also in the field of disease, in which there is a general deviation from the physiologic state.

I will endeavor to describe in a few words the development of the work of the Master, who made such an outstanding contribution to recording the curves which illustrate in a real and exact manner the electromotor phenomena observed during the contraction of the heart. In studying this evidence and in developing new techniques, he made intelligible the functions of the healthy and of the diseased heart. A development of this kind could only originate with a man who was not only well based in the sciences but also had the necessary human qualities which permitted him to make use of his knowledge in clinical science and thereby to give aid to his fellow man. The pure physiologist, and with him the philosopher, were able at one bound to traverse the space separating the pure from the clinical sciences.

Before turning to the work of Einthoven in the field in which he was the great pioneer, I will refer briefly to the work of Matteuci, in 1843, and that carried out by Koëlleker and Müller, in 1856. They were able to show that the contractions of the heart in the pigeon, the tortoise, and the frog produced an electrical current. Furthermore, demonstration of the action current of the heart in situ was made by Marey, in 1876, and by Waller, in 1877, at which time they used the capillary electrometer, which Lipman invented in 1873. In 1877, Waller was able to show that the electrical current originating from contraction of the heart spread throughout the body, both in animals and in man, and could thus be recorded on the external surface. Waller was responsible for developing the outline indicating the method of spread, which is known to us all.

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About the year 1900, Einthoven began to use the capillary electrometer in his research. This apparatus was at that time the most satisfactory known. It was aperiodic, but had too great an inertia to permit study of the phenomena observed.

In the address which he gave at Dordrecht, in 1893, on new methods of clinical examination, Einthoven pointed out that it was necessary to correct the readings obtained with this apparatus. He demonstrated methods with which correct readings could be obtained and was one of the first to make use of physical and mathematical corrections to give curves identical with those which were obtainable later from more satisfactory apparatus. It was he who in 1893 was the first to show an electrocardiogram illustrating ventricular activity, but only in 1895 was he able to add to this a tracing illustrating contraction of the auricle and the U wave. Until that time the action currents, now recognized for the first time, had been too weak to be registered by the techniques previously employed. It was at this period that he attached the letters P,Q,R,S,T, and U to the different waves which make up the electrocardiogram and thus for the first time brought this terminology into use in this way.

If it is true that the tracings obtained with the capillary electrometer were really representative, after correction, of the action current, it is also true that the construction of these tracings was difficult for many theoretical and practical reasons.

The Master devoted all his efforts to the construction of an apparatus which would give reliable curves. In this effort he had to overcome many well-recognized physical difficulties, for, as he himself said, the apparatus was required to be sensitive to many electrophysiologic changes and at the same time to be capable of numerous changes of direction.

In 1901, in the *Archives Néerlandaises des Sciences Experimentales*, Einthoven described the birth of the string galvanometer in a paper entitled "A New Electrocardiograph."

Again, in 1903, in the *Proceedings of the Koninklijke Academie D'Amsterdam*, he made known the first results of the application of this new apparatus in recording cardiac activity in man; the title of his paper was "The String Galvanometer and the Human Heart."

On a second occasion, in 1903, he published an article "Die Galvanometrische Registrierung des menschliches Elektrocardiogram, zugleich eine Beurteiling der Anwendung des Capillär-Elektrometers in der Physiologie." This appeared in *Pflüger's Archives für die gesamte Physiologie*. He said, "I have tried to find a means of avoiding the construction of a new curve which would be a corrected curve, if one continued to use the capillary electrometer. After much study, I have constructed an apparatus which meets many requirements. It is specially designed to give a direct registration from the human electrocardiogram which will give true readings."

About the same time a galvanometer of similar construction, containing a thread-like conductor lying in a magnetic field, was designed by Ader; this was in 1897. Einthoven has made known, with all his regard for justice and dignity, that he was quite unaware of the construction of this French apparatus when he developed his own string galvanometer. In the series of publications and communications he has made clear to us his lines of thought, the logical sequence of his reasoning, and the mathematical and physical approach to the problem. He gave us, in fact, all the information required for an understanding of the development and the construction of this wonderful instrument which he presented to us. It was in this way that it came so rapidly into use, both in pure science and in clinical and medical studies. It is evident that this apparatus could be used not only for the study of action currents of the heart, but also for an understanding of the activity of any organ in which an action current developed. Slight modifications of the apparatus could be made according to type of organ studied, physical characteristics of phenomena analyzed, and research accomplished.

In March, 1912, Einthoven read to the Chelsea Clinical Society his outstanding and famous communication entitled "The Different Forms of the Human Electrocardiogram and Their Significations." On that occasion he propounded the rule which bears his name—$D_{II} = D_I + D_{III}$. This

rule is exact when the points of derivation arise from the apex of any triangle, whatever its shape may be. To verify this rule it is necessary to take leads at one and the same time from each of the points involved. Therefore, one is obliged to make sure that one has taken readings of the potentials simultaneously from each lead. For the reasons given, he developed methods which made it possible to obtain simultaneous inscription of two or more leads. It is difficult, in fact, to obtain with any certainty synchronous points if the leads are registered separately. He developed his concept of the functions of the equilateral triangle. In this concept, one assumes that the heart lying in the human body may be considered as the source of punctiform electrical activity, situated in the middle of a homogeneous plane which has the shape of an equilateral triangle. From the angles of this triangle (R = R.A., L = L.A., F = L.L.) the current is led to the galvanometer. The resultant of the differences in potential may be represented by an arrow which points in a direction controlled at any moment by the contraction of the heart and passing through the central point which represents the heart. This arrow makes an angle α with the R.L. side of the triangle. In the method employed it is possible to discover at any moment the direction of the manifest resultant of the differences in potential and likewise to estimate the value of the manifest difference in potential of the heart at any moment.

A little later, in 1913, in association with Fahr and De Waart, he published an article which became famous. This appeared in *Pflüger's Archives für die gesamte Physiologie* and was concerned with the direction, the manifest value of the potentials in the human heart, and the influence of the position of the heart on the shape of the electrocardiogram. In this article he further elucidated the observations made before the Chelsea Clinical Society in 1912, and added some fresh material.

In all of his publications, lectures, and conferences he gave us in a masterly manner his views on the fundamental nature of the phenomena which were illustrated in the electrocardiogram and explained the factors which gave rise to the shape of the electrocardiogram both in health and disease. He made it quite clear that the P wave arises in the auricle, and that the Ta wave also derives from the auricle, whereas the complex Q-R-S and the T wave are related to ventricular activity.

He noted that when the S-T interval is isoelectric, all the ventricular musculature is in a state of contraction. If this contraction first ceases in the whole ventricular mass, no T wave is seen, and should a T wave be found, it indicates some asynchronism or a certain degree of asymmetry of ventricular contraction. This occurs when contraction in one part of the ventricles is slightly longer than contraction in the other part.

The essential qualities of the electrical phenomena related to the electrocardiographic tracings were regarded by Einthoven from two different standpoints. In the first theory he considered the heart as an electrical unity, so that any activity of the base of the heart would give rise to a negative reading of an electrode at the base and reciprocally. This theory might be described as that of "scattered differences of potential."

But from Lewis' work, which was explained in the Mellon Lecture, it could be shown that an electrode placed on the basal part of the heart could give a negative or a positive reading, which depended on stimulation of the basal tissues, starting in the former case at the basal side of the tissue and in the latter case at the apical side. This being proved, it was necessary to reconsider the first theory and to avoid speaking of "scattered differences of potential" and to substitute the description "limited differences of potential." Evidently it was not the anatomic position of the excited tissue which controlled the shape of the electrocardiogram, but rather the direction followed by the excitation. It was no longer possible to consider the heart as an electrical unit, and it became necessary to regard it as being made up of a large number of small microscopic structures, each of which was more or less independent. I will give the words used by Einthoven, and it was only after conversations with Sir Thomas Lewis that Einthoven and Lewis came to this conclusion.

In the Mellon Lecture, Lewis stated, "I suggested to Einthoven that it was neces-

sary to consider the fibres of the myocardium as individual units to make the facts agree with the generally accepted theory of excitation of muscles and nerves." In this way the multiplicity of cardiac generators was finally recognized.

It is evident that the term "manifest," which was then used in connection with the size and the resultant of the potentials at any moment, was an unfortunate one. It is not precise in his determinism. It is possible that one ought to take account, among other things, of the effect caused by the position of the heart in the thorax and to remember that the conducting media are not homogeneous. If my memory is correct, Einthoven was ready to admit these facts, but held them to be relatively unimportant. The system which he devised was, in a general way, quite satisfactory.

All the classic works on physiology did not suffice to satisfy Einthoven, who believed that the principal reason they existed was to contribute to the betterment of the state of health of mankind by providing a deeper knowledge of physiology and physiopathology. He was in contact with physicians and tried at all times to keep them informed of the nature of his work and of the results of his experiments, so that new fields of enquiry would be open to them.

He brought them into closer association with his work, showing them, if it were necessary, the benefit the patient would derive from this association. As proof of this I would like to draw your attention to the fact that electrocardiograms, as well as the heart sounds, also, were recorded from patients in the hospital, which was fifteen hundred meters from his laboratory. In this case, neither the patients nor the apparatus could be moved.

It was soon clear to Einthoven that the electrocardiogram of the diseased heart must vary greatly from that of the healthy heart. As he himself said, a few readings confirmed him in this opinion. The number of cases examined was insufficient. The most serious cases could not be taken to his laboratory. He thought it necessary, in the interest of the patient, to make an even more profound study of the physiopathology of the heart and to take readings from a larger number of sick persons. It was then that Professor Bosscha thought of running electric cables between the hospital and the laboratory fifteen hundred meters away.

I would like to make clear once again that the application of research work in the laboratory for the study of disease made continued progress as knowledge in this field increased. At no time were the sick absent from Einthoven's thoughts nor was his spirit indifferent to their interests. Einthoven was certainly a doctor in the widest sense of the word.

His friend Lewis was a man of the same pattern. The understanding between them could only be deep and sincere, when one bears in mind the intellectual, moral, and human qualities of these two great men.

In 1893, Einthoven had already registered a human electrocardiogram, although, at that time, he had only the capillary electrometer at his disposal. Until then, only five electrocardiograms from human beings had been registered throughout the world.

In 1900, in cooperation with Geluk and Blöte, he published a work under the title "Onderzoek van Eenige Lijders aan Hartzekten met de Capillair Electrometer." In 1900, also, with the help of K. De Lint, another of his works appeared, entitled "Über das normale menschliche Elektrokardiogramma und über die Kapillar-elektrometrische untersuchung einiger Herzkranken."

He drew our attention to the influence of respiration, position of the heart, vagal tone, the sympathetic nervous system, age, exertion, and the use of certain drugs upon the shape of the electrocardiogram in the healthy subject.

He studied various changes in the electrocardiogram caused by right or left hypertrophy, by disturbance of conduction between the auricle and the ventricle, and also by disordered conduction in the ventricles themselves. Furthermore, abnormal excitability of the myocardium was investigated, as were also auricular, nodal, and ventricular extrasystoles, together with the appearances shown in auricular fibrillation.

He also registered electrocardiograms in other disorders and even in congenital disabilities.

In his work, Einthoven likewise recorded the heart sounds, either alone or in association with other tracings.

Einthoven was not content to limit the use of the string galvanometer to the registration of electrocardiograms, and from 1904 onward he resumed work, already started, which was designed to register the heart sounds. In collaboration with Flohil and Battaerd, he described, in 1907, the methods used and the results obtained. The publication bore the title "Het Registreren van Menschelijke Harttoonen met de Snaargalvanometer." Some of the recordings described were made at a distance of fifteen hundred meters.

In 1907, working with Wieringa and Snijders, he described the third heart sound. It should be noted that in the course of a conference held at Dordrecht in 1893, he had already described the recording of faint sounds, particularly in the human and animal heart, which had been detected with the help of the capillary electrometer (linked with this, records were made either of the impact at the apex or of the carotid pulse, or else tracings were made from a mechanical cardiogram). He had described the most characteristic features. In the course of his investigations he was able to show that stimulation and contraction of the heart occur simultaneously.

The country may be proud to count among its children such a person as Einthoven.

Science rejoices when it is able to honor such men whose discoveries are for the good of humanity, and humanity is exalted by their moral and spiritual qualities. It is by the example of such men that the world continues to be beautiful and fruitful. In their modesty they do not think of themselves.

Einthoven
Commemoration address

*J. E. Jonkers**

On May 21, 1960, it was exactly 100 years since Willem Einthoven was born at Semarang, where his father was assistant municipal physician. We commemorate this fact in gratitude for all that Einthoven has given to the world. You and your colleagues, Mr. Chairman of this International Symposium held under the auspices of the University of Leiden, have all paid tribute to this great scholar by pausing to consider the phenomenal results of science in the field in which Einthoven was a pioneer. In the books *Willem Einthoven* by my colleague A. de Waart, and *Helden der Wetenschap* (Heroes of Science) by Dr. S. Hoogerwerf, I read a fascinating biography of Einthoven. Here we see Einthoven not only as a scholar but also as a person. He was completely lacking in bumptiousness. He was simplicity itself. He was still young when his father died. His sense of responsibility, which even in later years played such an important part in his life, led him, as the eldest son, to support his mother as much as possible. Einthoven was also aware of his shortcomings. He, the gifted scientist, did not neglect the study of the humanities. He studied history, music, and Latin. He knew by heart whole passages from Cicero's speeches. He enjoyed Horace's poetry, and as a tribute to him the last of the propositions in connection with his thesis was that in order to go through life undisturbed and to achieve something it is necessary to make the most of one's gifts and one's ability. Herein, to my mind, lies the secret of his great career as a scientist, quite apart from his particular aptitude. He was persevering and did not let himself be discouraged by opposition and disappointment. He was at the same time a sportsmanlike figure. Sports hardened him, and this was also an advantage to him in his career of scientific research. For that matter, sports were responsible for his first scientific publication. When he broke his right wrist in making a grand swing and had a considerable amount of trouble with it, he devoted himself to the study of the various hand and shoulder movements, as well as movement of the elbow joints, and wrote a number of articles on those subjects. He was at the time a medical student. It took him thirty years of diligent work to arrive at a definite theory concerning the electrocardiogram. Famous throughout the world are his string galvanometer and the vacuum string galvanometer, the originals of which are in the Dutch Museum of the History of Science. He also did very useful work in the field of radiotelegraphy. In collaboration with his son, who also had his father's perseverance, he brought about radiographic links with Malabar, with the aid of a refined version of the string galvanometer

Einthoven taught at our university from 1885 until his death. He was a professor at the age of 25. On September 28, 1927, his wife, who had helped him so much during his lifetime and in his career, closed the eyes of her dear husband. A great man went from us then. The world

*Prof. Jonkers is Rector Magnificus of Leiden University.

honored him in 1924, by awarding him the Nobel prize for physiology and medicine. The Netherlands honored him by making him a Commander in the Order of Oranje-Nassau. We honor the man who was an inspiration to so many by laying a wreath at the base of his statue. (See Fig. 1.) We are fortunate in having with us today several members of his family. He lies buried at the foot of the peaceful little green church at Oegstgeest, but his inspiring spirit lives on.

Fig. *1.* Laying of a wreath by the Rector Magnificus of Leiden University, Prof. Dr. J. E. Jonkers, at the bust of Einthoven, located in the hall on the second floor of the new physiology building at the Medical School of the University of Leiden. (Foto Bleuzé, J. Holvast, Leiden.)

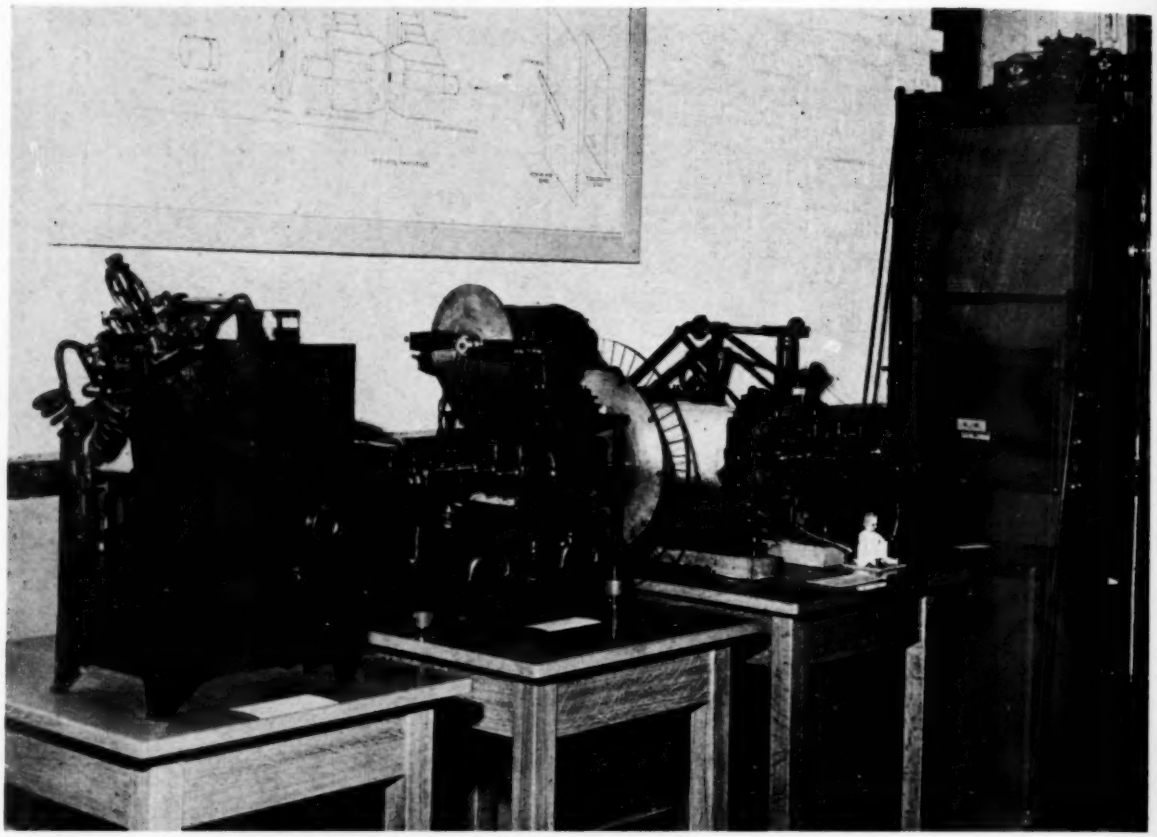

Fig. 2. The original electrocardiograph of Einthoven on display in the Museum of Science of Leiden. (Foto Bleuzé, J. Holvast, Leiden.)

After the reception following the Rector's speech many participants went to the Museum of Science to see the original first string galvanometer and other apparatus from Einthoven's laboratory (see Fig. 2).

Clinical communications

Atrial septal defect and the mechanism of shunt

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Over many years there has been much ingenious experimentation[1-4] and speculation[5,6] as to the mechanism of production of the shunt in subjects with atrial septal defects. The problem has recently been ably reviewed,[7] so that it will be reviewed again here only as it applies directly to the discussion. The present paper attempts a statistical approach to the mechanism of shunt, from data acquired during cardiac catheterization of human subjects with atrial septal defect.

Material and methods

From a series of diagnostic catheterizations, 24 subjects with atrial septal defects were selected in whom catheterization data included satisfactory pressure records, apparently reliable estimations of oxygen saturation in the required areas, and in whom no defects were known to exist other than an atrial septal defect. No subject who fulfilled the above criteria was excluded from the present analysis.

During catheterization, children under 12 years of age were anesthetized by rectal anesthesia, and adults were awake and without premedication. Oxygen saturations were determined by the Waters-Conley oximeter, which was recalibrated in each patient by the Van Slyke determinations of the oxygen content of systemic and pulmonary arterial blood, and which calibration curve is constructed over many months and from many subjects. Pressures were measured with Statham strain gauges, and recorded on either the Sanborn Poly-Viso or the Waters photographic recorder. Mean pressures were determined by electrical integration on the Sanborn machine, by slow period galvanometers on the Waters recorder, and checked by planimetric integration when required or when satisfactory mean pressures were not obtained by the above-mentioned methods. Oximetric and pressure measurements were done consecutively through the same cardiac catheter, and, hence, depend on the existence of a "steady state" in order to be compared. End-diastolic pressures were measured at the point of rapid systolic upsweep on the ventricular pressure tracing and are taken as the average value for each cardiac cycle throughout two respiratory cycles. Zero reference point for pressure was taken as the mid-point of the anteroposterior chest diameter in the region of the heart. Oxygen consumption was

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Table I. *Atrial septal defect and shunt*

Catheterization number	*Age, Sex*	*Surface Area (M.²)*	*Heart Rate*	*Arterial mean pressure (mm. Hg)*		*Systolic pressure (mm. Hg)*		*End-diastolic pressure (mm. Hg)*	
				Systemic	*Pulmonary*	*LV*	*RV*	*LV*	*RV*
1179	28, F	1.68	80	81	19	103	33	8.9	6.3
1126	36, F	1.46	73	91	61	119	99	9.6	7.0
1159	47, F	1.54	92	155	25	212	45	11.5	8.6
1183	35, F	1.44	100	125	18	160	35	8.7	5.1
1143	7, F	0.91	85	80	18	96	25	8.0	6.3
1125	4, M	0.82	124	82	24	94	38	9.0	9.0
494	19, M	1.81	64	84	20	114	41	11.5	7.1
609	35, F	1.76	98	87	27	114	46	9.0	7.0
596	28, F	1.54	84	91	15	106	27	9.2	9.4
106	14, M	1.83	83	109	18	105	40	9.2	6.4
885	34, F	1.63	75	93	15	108	33	9.2	7.9
374	25, M	1.92	66	98	20	136	40	16.0	12.6
399	24, M	1.78	92	108	103	118	132	9.7	6.6
635	20, F	1.42	76	96	22	105	35	15.8	10.9
1231	4, M	0.71	118	92	12	109	45	9.4	7.5
1232	8, F	1.03	108	91	18	110	30	7.8	4.3
141	9, F	0.89	116	107	14	110	30	8.6	4.5
233	4, M	0.71	128	56	20	96	28	10.9	5.9
382	7, F	0.81	95	82	15	88	29	7.7	2.3
137	9, F	0.76	125	62	141	108	204	2.7	6.1
133	27, F	1.77	77	91	15	106	33	9.1	6.1
662	3, M	0.61	146	72	24	89	36	7.5	6.3
1237	4, F	0.79	106	86	16	112	35	8.8	4.3
1296	36, F	1.47	80	95	69	115	115	8.4	6.6

measured by collecting the expired air in a Tissot spirometer and analyzing the expired gas for oxygen and carbon dioxide by the method of Scholander. Indicator dilution curves, utilizing indocyanine green dye, the Waters-Conley cuvette oximeters, and recorded on the Waters photographic recorder, were an important part of many of the diagnostic studies.

Calculation of pulmonary and systemic blood flow and the size of the shunts have been done by standard formulas.[8] The oxygen content of mixed venous blood, for the purposes of calculation, was assumed to equal the oxygen content of superior vena caval blood plus two times the oxygen content of inferior vena caval blood divided by three, on the assumption that two thirds of the blood enters the right atrium from the inferior vena cava.[4] Pulmonary venous blood was assumed to be 95 per cent saturated unless direct measurement of pulmonary venous blood indicated a higher saturation than this, in which case the higher saturation was utilized for calculations. Left and right ventricular work were calculated from the standard Starling formula as mean arterial blood pressure times flow. Resistances were calculated in centimeter-gram-second units by the usual formulas.

Results

The results are summarized in Tables I and II for the 24 subjects concerned in the main body of the statistical data. In 18 subjects, for some of whom hemodynamic data are included in this report, and in whom the size of the atrial septal defect was determined at operation, the "r value" for the correlation between the size of the defect and the amount of left-to-right shunt was $+0.29$ ($p > 0.1$). The pressure gradient from the left atrium to the right atrium, when compared with the left-to-right shunt, indicated a correlation coefficient of -0.04 ($p > 0.1$). The gradient between the end-diastolic pressure of the left and right ventricles, when correlated with the shunt, indicated a correlation coefficient of $+0.38$ ($p < 0.1$). However, the left ventricular systolic pressure minus

Atrial mean pressure (mm. Hg)		*Blood flow index (L./M.² BSA)*		*Stroke volume index (M.²BSA)*		*Ventricular work index (Kg.M./min./M.² BSA)*		*Total peripheral resistance (dynes cm.⁻⁵ sec.)*	*Pulmonary vascular resistance (dynes cm.⁻⁵ sec.)*
Left	*Right*	*Systemic*	*Pulmonary*	*LV*	*RV*	*LV*	*RV*		
7.0	6.0	6.0	17.4	75	218	6.6	4.5	675	33
6.0	5.0	3.3	5.1	45	70	4.1	4.2	1,507	590
6.7	8.0	3.2	11.4	35	124	6.8	3.9	2,487	83
6.0	6.0	5.1	14.1	51	141	8.6	3.5	1,365	47
6.0	6.0	4.6	7.7	54	91	5.7	1.9	1,504	137
8.0	8.0	4.8	5.4	39	44	5.4	1.8	1,654	289
10.0	5.0	4.6	7.5	72	117	5.3	2.0	766	59
9.2	9.2	3.5	13.8	36	141	4.1	5.1	1,114	59
5.7	5.2	3.0	6.5	36	97	3.7	1.3	1,693	74
6.5	5.7	4.6	17.2	55	207	7.1	5.1	1,081	29
6.0	5.0	3.6	5.6	48	75	4.6	1.3	1,194	79
10.0	8.5	3.2	9.1	48	138	4.3	2.2	1,275	46
4.5	4.5	4.7	1.6	51	17	7.0	2.3	1,013	2,764
9.0	9.0	3.3	10.9	43	89	4.3	3.3	1,633	67
5.7	4.5	5.2	9.3	44	79	6.5	1.3	1,986	76
7.0	5.0	3.6	9.8	33	91	4.5	2.4	1,960	87
2.6	2.9	4.1	8.3	35	72	6.0	1.6	2,344	123
6.2	5.2	5.9	14.8	46	116	4.5	4.0	978	105
5.5	4.8	3.1	7.7	33	63	3.3	1.6	2,770	122
5.5	4.5	5.9	4.9	47	39	4.9	9.2	1,110	2,908
5.1	3.1	2.8	10.5	36	136	3.3	2.2	1,498	43
7.5	6.5	6.1	11.4	42	79	6.0	3.7	1,550	190
4.0	4.0	6.9	9.2	65	87	8.1	2.0	1,261	132
4.5	4.0	3.1	1.8	39	23	4.1	1.7	1,640	1,948

the right ventricular systolic pressure correlated more closely with the left-to-right shunt ($r = +0.61$, $p < 0.001$). The systemic minus pulmonary mean arterial pressure, when compared with the shunt, indicated an "r value" of $+0.48$ ($p < 0.02$). There was a significant correlation between the end-diastolic pressures in the left and in the right ventricles ($r = +0.68$, $p < 0.001$); however, there was no correlation between right ventricular end-diastolic pressure and the right ventricular stroke index ($r = +0.09$, $p > 0.1$), or between the left ventricular end-diastolic pressure and the left ventricular stroke index ($p < 0.08$, $p > 0.1$). The left ventricular work index minus the right ventricular work index did not correlate significantly with the left-to-right shunt ($r = 0.11$, $p > 0.1$). The systemic minus the pulmonary vascular resistance, when correlated with the left-to-right shunt, indicated a correlation coefficient of 0.50 ($p < 0.02$). If an index of distensibility for each ventricle be calculated by dividing its stroke index by its end-diastolic pressure, the difference between these calculated "distensibility factors" may be related to the left-to-right shunt. When this is done, the "r value" was found to be $+0.83$ and $p < 0.001$.

Discussion

There is no doubt that on some occasions, during heart failure with pulmonary congestion and edema, pulmonary venous blood is desaturated,[9] and under these circumstances, calculations based on the assumption that it is fully saturated would indicate a right-to-left shunt. The inclusion of data from such subjects would vitiate any attempts to relate pressure flow measurements. However, none of the present subjects had pulmonary edema, and right-to-left shunts have been demonstrated in many compensated subjects with atrial septal defect.[4] Furthermore, it has been stated that in atrial septal defect the pulmonary venous blood may be desaturated from excessive flow alone.[10] Others have doubted that this is a significant factor and have presented data to show that pulmonary venous desaturation is

Table II. *Correlations in subjects with atrial septal defect*

	"r Value"	*"p Value"*
Related to Shunt:		
L → R shunt index with left minus right atrial mean pressure	−0.044	>0.1
L → R shunt index with left minus right ventricular work index	−0.109	>0.1
L → R shunt index with atrial septal defect size	+0.286	>0.1
L → R shunt index with left minus right ventricular end-diastolic pressure	+0.375	<0.1
L → R shunt index with systemic minus pulmonary mean arterial pressure	+0.478	<0.02
L → R shunt index with systemic minus pulmonary vascular resistance	+0.495	<0.02
L → R shunt index with left minus right ventricular systolic pressure	+0.606	<0.001
L → R shunt index with right minus left ventricular "distensibility"	+0.830	<0.001
General Correlations:		
Right ventricular stroke index with right ventricular end-diastolic pressure	+0.087	>0.1
Left ventricular stroke index with left ventricular end-diastolic pressure	+0.080	>0.1
Left with right ventricular end-diastolic pressure	+0.680	<0.001

unusual,[7] and although minor right-to-left shunts may rarely be calculated for this reason, it seems unlikely that this is a common error. Certainly, this explanation is unsatisfactory for the right-to-left shunts revealed on indicator-dilution curves.[4] The presence of streaming of blood in the right atrium is undoubted; and it has been shown that, in general, blood from the inferior vena cava tends more to cross an atrial septal defect than does that from the superior vena cava.[4,11] The demonstration of such streams, their direction of flow, and the fact that dye contained in them may cross the septum still, however, does not answer the basic hemodynamic question of the determinants of flow through the defect. The postulate that the relative atrial positions determine the flow of blood through the septal defect[1] seems to have been disproved by the demonstration that change of position of the atria by placing the subject in head-down tilt fails to eliminate the shunt.[12]

The absence, in the present series, of a significant correlation between the size of the atrial septal defect as measured at operation and the amount of shunt is expected and has been discussed by others.[5,13] Indeed, if the patients in whom the shunt was reversed were subjected to operation, the present correlation would be even less, since it is well known that the predominant shunt may be in either direction. It should be emphasized that measurement and comparison of atrial mean pressures is difficult, because (1) the pressure is small and small errors are magnified percentagewise, (2) pressure varies considerably with respiration, as well as cardiac action, and (3) the pressures in the two atria have not been measured simultaneously. There seems no doubt that, if the atrial septal defect is sufficiently small, its size will limit the shunt, and under these circumstances a considerable pressure gradient may be measured across the defect. This gradient may even reach the normal interatrial gradient.[2,3,7] In those with larger defects, such as are known to exist in many of the present subjects, the mean pressure gradient between the left and right atria is very small, as was postulated by Barger and associates,[14] and in the present series does not correlate with the size of shunt. The present authors accept the fact that in order for blood flow to occur through an orifice (such as an atrial septal defect) there must be a pressure gradient across the orifice; however, from the present data this gradient seems to be so small that it has not been measured sufficiently accurately to be demonstrated. Other investigators have had a similar lack of success in their endeavors to relate left and right atrial pressures to the shunt between the two atrial cavities,[4,7,9,15] and some have emphasized transient pressure gradients which cause significant shunting but are not reflected adequately in the mean left and right atrial pressures.[6] Although it is stated that Calazel and others[16] found a good correlation between the left and right atrial pressures and the direction of the shunt, study of their paper reveals that of the 9 cases reported, only two had

an uncomplicated atrial septal defect. Two had only a patent foramen ovale, in which presumably no left-to-right interatrial shunt occurs. The other cases had pulmonic stenosis, tricuspid atresia, mitral stenosis, and transposition of the great vessels, so that it is doubtful whether data derived from such subjects may be applied to the problem under discussion. The data from animals with experimental atrial septal defects indicate that, even when a gradient can be measured between the atria, it exists only as long as the heart continues functioning and vanishes when cardiac arrest is induced.[2] Hence, the primary driving force of the interatrial shunt resides in some phase of cardiac activity.

Unfortunately, the measurement and comparison of ventricular end-diastolic pressures are among the least accurate in any study. This is partly because the pressure levels and differences involved are so small that a small error becomes magnified percentagewise, and partly because the exact point at which an "end-diastolic" pressure should be measured on the curving junction of systole and diastole on a ventricular pressure curve becomes a matter of opinion. In the present study these were all measured and rechecked by the same individual so as to secure greater uniformity. Still, complete accuracy remains unobtainable. It is of some interest that the end-diastolic pressures in the two ventricles correlate so closely ($r = +0.68$) with each other. Presumably this is because venous pressure on each side of the heart equilibrates through the interatrial defect. The difference between the end-diastolic pressures of the two ventricles failed to correlate well with the shunt, indicating that again the study of pressure alone is probably inadequate to explain the shunt.

It has been postulated[7,14,15] that a sizable defect between the two atrial chambers reduces them to a common chamber, and that the proportions of flow out of this common chamber are determined by which ventricle is most easily filled. Or, in other words, the diastolic distensibility of the ventricles determines the size of shunt. This appears to be confirmed by the present data ($r = +0.83$). A logical extension of this postulate is that the ventricular systolic pressures, the mean arterial pressures, and the systemic and pulmonary vascular resistances are related to the size of the shunt because they help to determine the thickness of the ventricular walls and, therefore, their distensibility. The statistical relation between the ventricular distensibility and the shunt must be considered in light of the fact that any calculation of distensibility of a ventricle must include its stroke volume. The calculated distensibility is, therefore, mathematically related to the shunt, and a portion of the correlation between the shunt and the calculated distensibility of the ventricles is spurious. It should also be pointed out that to whatever extent the resistance to flow at the atrial septal defect limits flow, the correlation between ventricular distensibility and shunt will be reduced. Nevertheless, when all these factors are considered, it seems reasonable that the calculated relation between ventricular distensibility and the shunt is significant.

Conclusions

1. A statistical study is presented of 24 subjects in whom an atrial septal defect, and no other defect, was demonstrated at cardiac catheterization.

2. The various parameters related to the left-to-right shunt, in line of descending order of correlation between measured or calculated parameter and shunt, are the following: (a) right ventricular as compared to left ventricular distensibility, (b) left ventricular minus right ventricular systolic pressure, (c) systemic minus pulmonary vascular resistance, (d) systemic minus pulmonary mean arterial pressure.

3. The degree of mathematical relation between some of these parameters requires that allowance be made for spurious mathematical correlation.

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Urinary excretion of catecholamines and their metabolites in pheochromocytoma

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In recent years it has been established that the major urinary metabolites of circulating epinephrine (E) and norepinephrine (NE) are 3-methoxy-4-hydroxymandelic acid (MOMA) and the respective 3-methoxy amines, metanephrine (MN) and normetanephrine (NMN).[1-3] Since these metabolites appear in the urine in much larger amounts than the parent amines, convenient methods for their determination should be of value in the diagnosis of pheochromocytoma. Current interest is centered chiefly on the determination of MOMA, the major urinary metabolite of infused catecholamines. Although most of the methods for assaying this compound[4-8] seem to have little technical advantage over the determination of free catecholamines, at least two simplified procedures for the detecting of an increased excretion of MOMA have been described.[9,10] Marked elevations of the excretion of MOMA in cases of pheochromocytoma have been demonstrated with each of these methods. It has not been established, however, that urinary MOMA is actually a more reliable index than the free catecholamines in distinguishing patients with pheochromocytoma from the remainder of the hypertensive population.

Recently, spectrophotometric methods for the determination of urinary MOMA[11] and for the assay of total metanephrines (NMN plus MN)[12] have been developed in this laboratory. Measurements of these metabolites, as well as the urinary catecholamines, have now been performed in a large number of patients with essential hypertension and in 23 patients with pheochromocytoma. The present report describes the accuracy with which each of these three indices of catecholamine production—the free catecholamine excretion (NE plus E), the total metanephrine excretion (NMN plus MN), and the MOMA excretion—served to detect pheochromocytoma in this series of patients. Since in our experience the assay of total metanephrines has been the most convenient method for screening purposes, certain aspects of this procedure are considered in detail.

Methods

Twenty-four-hour specimens of urine were collected in 10-15 ml. of 6N hydrochloric acid and stored at 0°C. Specimens from 2 of the patients with pheochromocytoma (Cases 2 and 9) were in storage for 48 months prior to the time of complete assay, but the remainder of the specimens

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were stored for 30 months or less. NE and E have been found to be stable under these conditions for at least 4 years, and the methylated metabolites for at least 1 year, these being the longest time periods tested to date. MOMA has been reported to be stable in urine for many months under similar conditions.[4]

Free catecholamines were determined by a modification of the trihydroxyindole method, using iodine as the oxidizing agent.[13] Both NE and E were measured in all specimens from patients with pheochromocytoma, but the values to be reported are for combined NE plus E. These values are not corrected for an average 87 per cent recovery.

Total urinary metanephrines (free plus conjugated, NMN plus MN) were determined essentially by the method of Pisano,[12] with several minor alterations. The modified procedure is as follows: An aliquot of urine equivalent to 0.5 per cent of the 24-hour volume (4-15 ml.) is added to a 40-ml. centrifuge tube and acidified with 0.1 volume of 2N hydrochloric acid, giving a final pH of less than 1. The tube is placed in a bath of boiling water for 20 minutes to hydrolyze conjugated NMN and MN. After cooling, two drops of 0.1 per cent bromcresol purple are added as an indicator, and the pH is adjusted to 6.0-6.5 with 1N sodium hydroxide. The sample is diluted to 30 ml. with distilled water, and any sediment is removed by centrifugation. The supernatant urine is passed over a 1.2 by 5-cm. column of Amberlite CG-50* buffered at pH 6.5 as described previously.[12] The flow rate must not exceed 1 ml. per minute. The column is then washed with 20 ml. of deionized water and eluted with 10.0 ml. of 4N ammonium hydroxide. To a 4.0-ml. aliquot of the ammonium eluate is added 0.1 ml. of 1.6 per cent sodium metaperiodate; this cleaves the side chain of both NMN and MN to yield vanillin. After 2 minutes, 0.1 ml. of 10 per cent sodium bisulfite is added to remove excess periodate ion. To a second 4.0-ml. portion of the eluate, which serves as a urine blank, is added 0.1 ml. of water and 0.1 ml. of 10 per cent sodium bisulfite. The amount of vanillin formed by periodate treatment is determined by measuring the optical density (O.D.) of the sample at 360 mμ with the spectrophotometer adjusted to zero O.D. with the urine blank. Under these conditions, samples of normal urine measured with a 1.0-cm. light path have an O.D. at 360 mμ of 0.070 or less. On the basis of the O.D. of standard solutions and the constant fraction of the daily urine volume assayed (0.5 per cent), a factor can be calculated for the direct conversion of the O.D. reading to total metanephrine excretion. On our instrument (Beckman DU spectrophotometer), total metanephrine excretion in milligrams per day of NMN equivalents (entire reading assumed to be due to NMN) is 18.8 × O.D. at 360 mμ. No correction is made for an average recovery of 84 per cent.

The absorption peak of vanillin formed in the assay of total metanephrines is at 347 mμ, but many samples of urine from patients without pheochromocytoma contain an unidentified material with an absorption peak at 333 mμ. The contribution of this interfering material to total absorbency at the vanillin peak of 347 mμ is often quite significant. Therefore, the sample is read at 360 mμ, where the absorbency of vanillin is 80 per cent of its peak value but that of the 333-mμ absorbing material is minimal. Every value over 1.0 mg. per day (O.D. at 360 mμ over 0.053) in patients without pheochromocytoma has been due to the presence of unusually large amounts of this 333-mμ absorbing material. For this reason all samples with an O.D. at 360 mμ greater than 0.053 are also read at 347 mμ and 333 mμ to determine whether the high reading is due to this interfering substance (peak at 333 mμ) or to vanillin (peak at 347 mμ). All patients with pheochromocytoma have had the typical vanillin peak of 347 mμ. Because of this interfering material and the low O.D. values in samples from patients without pheochromocytoma, the method should be considered quantitative only for excretion values higher than 2.0 mg. per day of NMN equivalents.

Urinary MOMA was determined as described in a separate communication.[11] In brief, the phenolic acids are extracted from a salt-saturated acidified aliquot of

*Amberlite CG-50, Type 2,200 mesh and over, from Fisher Scientific Company, Fair Lawn, N. J.

urine with ethyl acetate and returned to a small portion of 1M potassium carbonate. The MOMA in this extract is then converted to vanillin with periodate. After adjustment of the extract to pH 7.5, the vanillin is extracted into toluene and returned to 1M potassium carbonate. The O.D. at 360 mμ of the carbonate layer is then determined as in the procedure for total metanephrines. The recovery of added MOMA is quantitative.

Results

Patients without pheochromocytoma. In a series of 114 hypertensive patients who were not acutely ill the excretion of free catecholamines (NE plus E) was found to be 32 ± 18 μg per day (mean ± S.D.). The upper limit of "normal" for the ambulant hypertensive population is considered to be 100 μg per day. Only 2 hypertensive patients without pheochromocytoma have been encountered with values above this figure; their excretions of free catecholamines were 115 and 117 μg per day, respectively.

In a second series of 121 patients (91 with primary hypertension and 30 without hypertension) the excretion of total metanephrines (NMN plus MN) was 0.62 ± 0.28 mg. per day of NMN equivalents (mean ± S.D.). No statistically significant difference was found between the hypertensive and nonhypertensive groups, but the semiquantitative nature of the assay in this range makes this observation of questionable significance. The upper limit of "normal" for the excretion of total metanephrines is considered to be 1.3 mg. per day. Every value above 1.0 mg. per day, including those of 3 patients who had excretion figures considerably higher than those of the rest of the population (values of 1.6, 1.6, and 1.7 mg. per day), was due to the presence of an unidentified but easily recognizable substance which interfered with the determination (see Methods). No drugs were encountered which directly interfere with the assay. The ingestion of bananas, previously shown to increase the urinary excretion of conjugated catecholamines,[9] did not influence the excretion of the total metanephrines. Treatment of hypertensive patients with monoamine oxidase inhibitors, however, may increase the excretion values to levels as high as 2.2 mg. per day. This increase may persist to some degree for as long as 2 weeks after the enzyme inhibitor is discontinued.

In a series of 20 patients with primary hypertension the excretion of MOMA was found to be 3.7 ± 1.1 mg. per day (mean ± S.D.). The upper limit of the "normal" range for hypertensive patients is considered to be 6.0 mg. per day; one patient had a value above this figure (7.1 mg. per day).

Patients with pheochromocytoma. In each of the 23 patients with pheochromocytoma, MOMA was the major metabolite excreted in the urine; total metanephrines were next most prominent; and the free catecholamines comprised only a small fraction of the total excretion. Since the clearest indication of an abnormally high excretion value for a compound is the degree of elevation above normal rather than the absolute excretion in milligrams, the result in each patient is expressed as a multiple of the upper limit of "normal" for each assay. As shown in Figs. 1 and 2, two types of patterns of excretion were observed. In the first group (15 patients, Fig. 1) the relative increase above normal was greatest for the free catecholamines, next greatest for the total metanephrines, and least for MOMA. This pattern was relatively constant over a wide range of values. In the second group (8 patients, Fig. 2) the methylated metabolites were increased relative to normal more than the free catecholamines; the over-all pattern from patient to patient was more variable than in the first group.

From a consideration of the two groups as a whole, the comparative value of the three different assays in detecting the presence of a tumor may be summarized as follows: (1) A diagnostic elevation of all three indices of catecholamine production was found in 20 of the 23 patients. (2) In the patients who did not have a diagnostic increase in urinary excretion by all three tests (Cases 1, 2, and 4) the assay of free catecholamines was the only test which was diagnostic in all 3 patients. (3) The single test giving the largest relative increase over normal was either the assay of free catecholamines or the determination of total metanephrines, depending upon

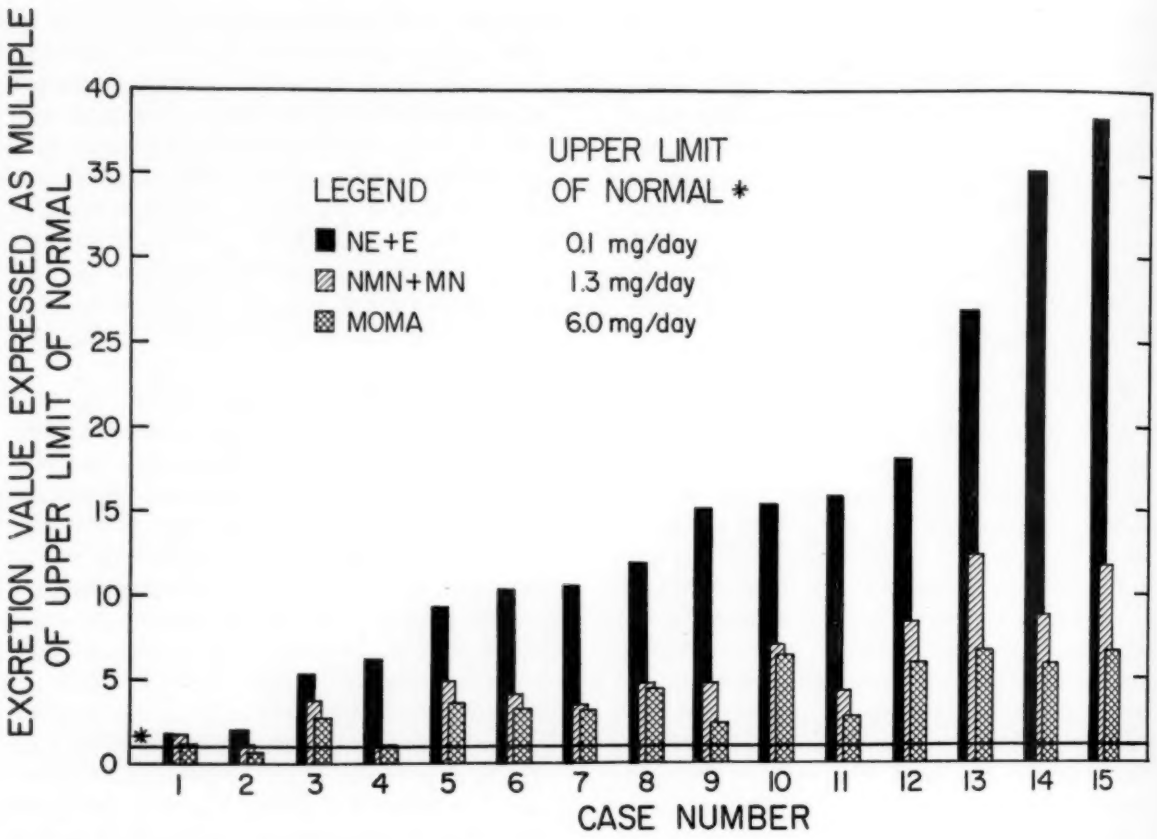

Fig. *1.* Pattern of excretion of urinary catecholamines and metabolites in 15 patients in whom the free catecholamines showed the greatest relative increase over the upper limit of "normal" (see text). The horizontal line marked with an asterisk represents the upper limit of "normal" for each assay. *NE + E:* Free catecholamines. *NMN+ MN:* Total metanephrines. *MOMA:* 3-methoxy-4-hydroxymandelic acid.

the pattern of excretion of the patient (Fig. 1 vs. Fig. 2).

Discussion

The findings of this study indicate that the determination of the free catecholamines or either of their major metabolites in urine provides an excellent chemical basis for the diagnosis of pheochromocytoma in most cases of the disease. This does not imply that each assay is of equal validity in an individual case. In one type of patient (Fig. 1) the determination of free catecholamines shows the greatest relative increase over normal. This assay is of particular value in patients with minimally secreting tumors (Cases 1-4). In the second type of patient (Fig. 2) the excretion of total metanephrines shows the largest relative elevation. Our interpretation is that considerable quantities of catecholamines are being methylated directly in the tumor in the latter group of patients. The relative excess of methylated metabolites in the urine could thus arise from a tumor which is releasing a mixture of cathecholamines and metabolites into the blood stream. The pattern of excretion of the first group, on the other hand, is believed to be the result of the release of relatively pure catecholamines from the tumor. Previous work from this laboratory,[15] demonstrating that pheochromocytomas may contain both NMN and catechol-O-methyl transferase, is compatible with the postulate that considerable metabolism of the catecholamines may occur directly in the tumor prior to their release into the circulation.

The determination of urinary MOMA might seem a priori to be the ideal chemical method of detecting patients with pheochromocytoma. However, the high range of normal for the excretion of this compound (up to 6 mg. per day) more than offsets the advantage of its being the major

urinary metabolite. Two cases in the literature are reported to have shown an increased excretion of MOMA at the time at which the value for free catecholamines was normal (Patient 23, Table III, in the series of Gitlow and associates,[4] and the patient described by Kraupp and associates[16]). It is quite possible that these patients were of the type shown in Fig. 2. If this is true, a determination of total metanephrines should have been at least as helpful as the MOMA excretion in establishing the diagnosis.

Because of its high degree of reliability and comparative ease of technical performance, the determination of total metanephrines is favored by us for the screening of hypertensive patients for the presence of pheochromocytoma. When the results by this test are equivocal, an assay of free catecholamines is indicated. On the basis of these general concepts, the following approach to diagnosis has been adopted in our laboratory:

1. A determination of total metanephrines is performed as part of the initial laboratory examination of each hypertensive patient. The phentolamine (Regitine) test,[17] formerly employed as a screening procedure, is no longer used. An excretion of total

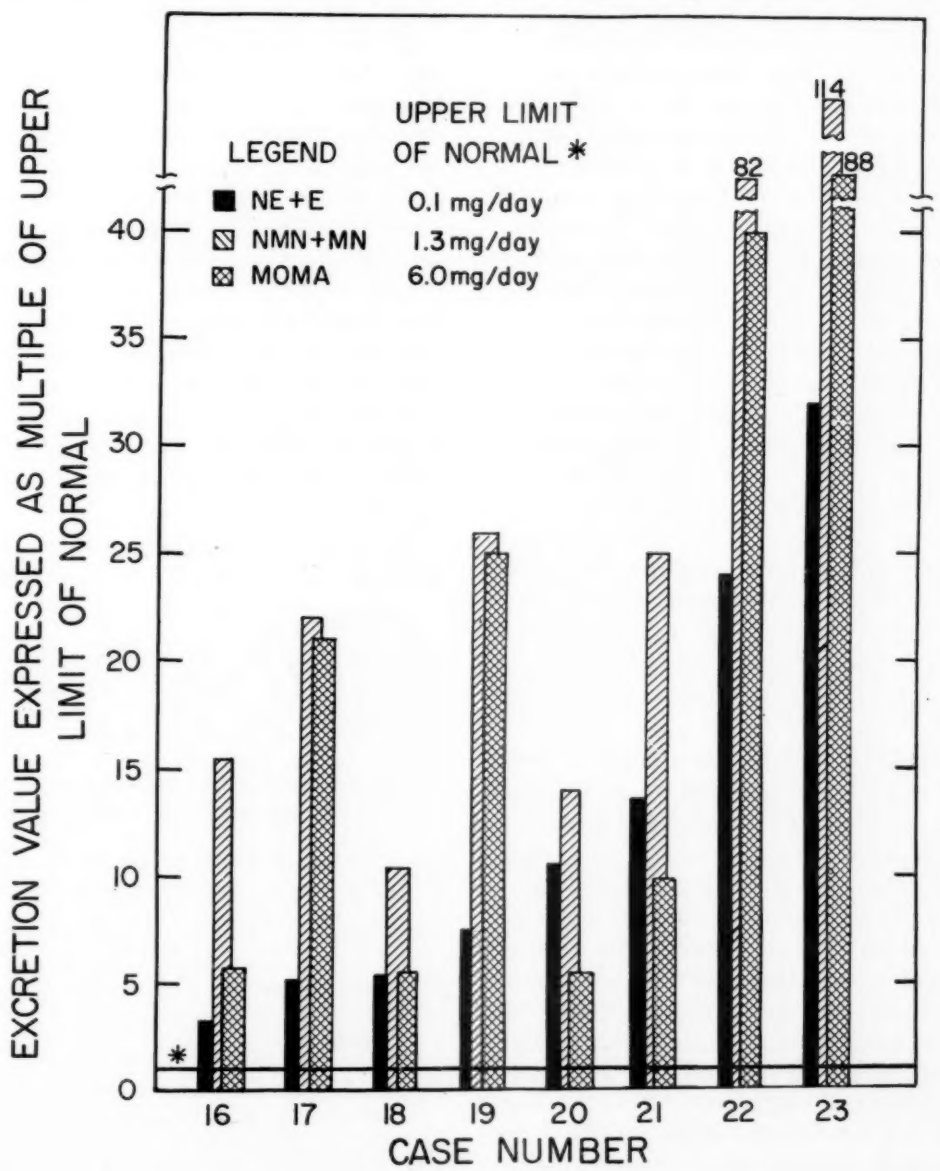

Fig. 2. Pattern of urinary excretion in 8 patients in whom O-methylated metabolites showed the greatest relative increase over "normal."

metanephrines of 1.0 mg. per day of NMN equivalents or less in a patient with sustained hypertension is considered to rule out pheochromocytoma, whereas a value of 2.5 mg. per day or higher for total metanephrines is considered to be diagnostic of pheochromocytoma.

2. Values between 1.0 and 2.5 mg. per day of NMN equivalents (6 per cent of patients without tumors in this series) are considered equivocal. This rather wide equivocal range is selected to minimize the chance of both false-positive and false-negative diagnoses. If the U-V spectrum is characteristic of vanillin (peak at 347 mμ; see Methods) or the value is over 1.3 mg. per day regardless of the U-V spectrum, a determination of free catecholamines is performed. If the U-V spectrum indicates the presence of interfering material (peak at 333 mμ), and the value is between 1.0 and 1.3 mg. per day, the free urinary catecholamines are determined only on strong clinical suspicion of pheochromocytoma.

3. In the patient with paroxysmal hypertension who has a normal excretion of total metanephrines and little or no elevation of blood pressure on the day on which the urine is collected, a timed specimen of urine is collected during a spontaneous paroxysm or after a histamine test[18] and assayed for free NE and E. Failure to demonstrate an increase in the excretion of free catecholamines during an elevation of blood pressure is considered to rule out pheochromocytoma. Conversely, a clear increase (at least twofold) in the excretion of either NE or E at this time supports the diagnosis.

The foregoing diagnostic approach has been followed for about one year. During this time, samples of urine from approximately 150 hypertensive patients who were clinically suspected of having pheochromocytoma have been studied and 10 cases of the disease have been proved. No known false-positive or false-negative diagnoses have occurred in this series of patients.

In most hypertensive patients, chemical tests of the urine clearly indicate the presence or absence of pheochromocytoma. The greatest diagnostic challenge is the rare patient with paroxysmal hypertension whose excretion values are increased only at the time of an attack, or the occasional patient with persistent hypertension who has only a borderline increase in the excretion of catecholamines or their metabolites. In such patients the clinical picture and the results of pharmacologic tests, as well as the urinary excretion data, must be carefully considered in arriving at a diagnosis.

Summary

Twenty-four-hour specimens of urine from 23 patients with pheochromocytoma and a large group of hypertensive subjects were assayed for free catecholamines (norepinephrine plus epinephrine), total metanephrines (metanephrine plus normetanephrine), and 3-methoxy-4-hydroxymandelic acid. Twenty of the 23 patients with tumors had a diagnostic increase in the urinary excretion of all catecholamine metabolites. In the other 3 patients the assay of free catecholamines was the single most reliable test. Because of its over-all reliability and ease of performance, the assay of total metanephrines is favored for screening hypertensive patients for the presence of pheochromocytoma. In the occasional patient whose value is equivocal by this assay, the determination of free catecholamines is considered to be the most helpful test in confirming or excluding the diagnosis.

We wish to acknowledge the excellent technical assistance of Miss Doris Watts in this study.

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Surgical implications of single coronary artery A review and two case reports

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Single coronary artery is a rare anomaly which usually is of no clinical significance.[4] In cardiac operations, however, the recognition of this anomaly may be of crucial importance. The present study describes the anatomic variants of single coronary artery, with emphasis on surgical implications. The literature is summarized since the publication of Smith's collective review in 1950, and two case reports are added.

Case reports

Case 1. A premature Negro female infant was delivered by cesarean section on Jan. 15, 1958. Her condition remained satisfactory until January 23, when poor feeding and lethargy were noted. On January 25, she developed respiratory distress, edema, and cyanosis. She did not respond to medical therapy and died on January 26.

At autopsy, the cause of death was attributed to congenital heart disease with cardiac failure, bilateral pleural effusion, and encephalmalacia of the thalamus. Examination of the heart revealed cardiomegaly and large ventricular septal defect. Microscopic examination of the heart demonstrated marked edema of the myocardium. There was a single ostium where the left coronary ostium normally is situated (Fig. 1). The single coronary artery divided into two main branches, 2 mm. from the orifice. The left branch followed the course of a normal left coronary artery, giving rise to the anterior descending branch and terminating as the circumflex branch. The right main trunk traveled the course of a normal right coronary artery and terminated as the posterior descending branch. An unusually large infundibular branch crossed diagonally from right to left across the outflow tract of the hypertrophied right ventricle.

Case 2. A Negro male infant, one of a pair of twins, was born on May 22, 1956. Both of the infants were discharged from the hospital on May 25. On June 3, the infant refused to nurse, and the following day his breathing became labored. He was rushed to the hospital but was dead on arrival.

At autopsy, the cause of death was attributed to congenital malformation of the heart, pulmonary congestion, and atelectasis. Examination of the heart revealed hypertrophy of the right ventricle, hypoplasia of the mitral valve, and dilatation of the pulmonary artery. The aorta was hypoplastic and stenotic. There was marked stenosis of the aortic valve, and only two cusps, anterior and posterior, were present. A single coronary artery ostium was located at the posterior cusp (Fig. 2). Arising from the ostium was a single coronary trunk which coursed around the left atrioventricular groove and continued to the right atrioventricular groove. Here its terminal branches coursed over the preventricular surface of the right ventricle. Anterior and posterior descending branches and marginal branches arose in a normal pattern of distribution.

Discussion

By definition, a single coronary artery arises by one ostium from an arterial trunk and nourishes the entire myocardium, re-

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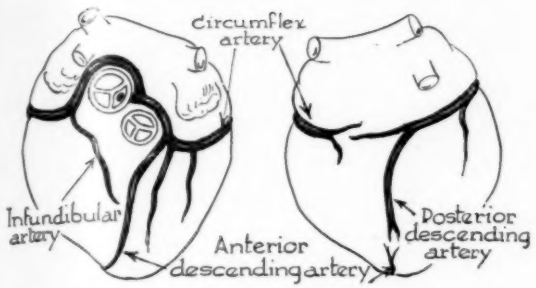

Fig. *1.* Drawing of coronary distribution in Case 1. The single coronary artery arises at the usual site of origin of the left coronary artery. The branch supplying the right heart passes behind the aorta. An hypertrophied infundibular branch arises from the right coronary artery.

gardless of the distribution of the branches. Smith,[17] in 1950, found 45 cases in his review of the literature. He classified these into three anatomic types. *Type 1:* A single coronary follows the course of only the normal right or left coronary artery. *Type 2:* A single coronary artery arises from one ostium but divides so that branches are present in the distribution of both the right and left coronary arteries. *Type 3:* A single coronary artery has so atypical a distribution that it cannot be compared with the right or left coronary artery. The latter type had been described previously by Krumbhaar and Ehrich.[10] Smith also included in this third group those cases in which insufficient data were given. We have designated such cases as *Type 4.*

The present review adds 25 new cases, bringing the total to 70 cases of single coronary artery. Data on the cases reported since 1950 are presented in Table I.

Several mechanisms of development of this anomaly have been presented.[10,14,15] It is generally agreed that a single coronary artery is the result of one of two developmental anomalies: (1) absence of a coronary artery anlage (Type 1), or (2) misplacement with fusing of the coronary artery anlagen (Type 2).

The presence of a single coronary artery in congenitally malformed hearts may present a considerable problem during open-heart operation. Recent reports have appeared on the accidental division of an anomalous single coronary artery during ventriculotomy for the correction of tetralogy of Fallot. Kirklin[9] reported a case in which an unrecognized left coronary artery arose from a single right coronary artery and crossed the outflow tract of the right ventricle. This branch was divided during the ventriculotomy. Senning[16] reported a case in which the entire left coronary artery arose from the right coronary artery and crossed the region of the infundibular stenosis. This branch was divided during the right ventriculotomy. Friedman's[6] case was similar to those of Kirklin and Senning (Fig. 3). The left coronary artery was divided when the incision was made in the right ventricle. In all three cases the patients died immediately upon division of the left coronary artery. These three cases are examples of Type-2 single coronary artery, the left coronary artery arising from a single right coronary artery.

In the majority of cases with this anomaly the distribution of major coronary vessels is such that the usual type of incision may be made with impunity. However, in a few instances a major branch crosses in front of the pulmonary artery and

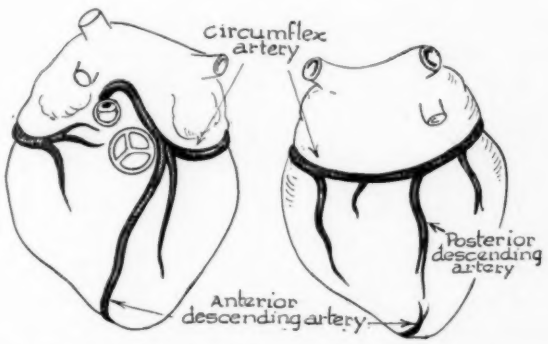

Fig. *2.* Drawing of the coronary distribution in Case 2. The single vessel arises from an atretic aorta, encircles the heart from left to right, and supplies the entire myocardium.

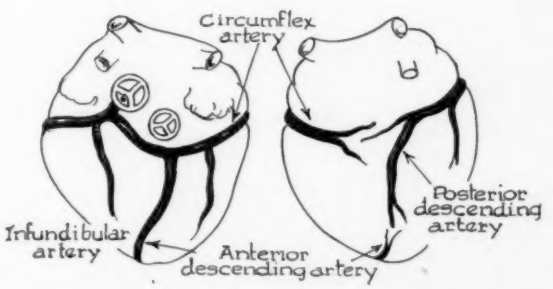

Fig. *3.* Drawing of single coronary artery distribution with major vessel passing in front of the pulmonary artery. The usual incision of right ventricular outflow tract and pulmonary artery would result in division of this vessel.

Table I. *Twenty-five cases of single coronary artery reported in the literature since 1950*

Number	*Age*	*Sex*	*Single artery present*	*Weight of heart (grams)*	*Type**	*Autopsy*	*Year*	*Author*
1.	9 days	M	R	—	4	CHD	1956	Alexander[1] (Case 5)
2.	11 days	F	L	—	2	VSD	1960	Longenecker, et al.
3.	14 days	M	L	—	1	Hypoplasia of mitral valve; aortic stenosis; bicuspid aortic valve	1960	Longenecker, et al.
4.	7 wk.	F	R	54	3	Coarctation of right pulmonary artery and aorta; bicuspid aortic valve	1959	Raekallio[13]
5.	4½ mo.	F	R	—	2	Transposed great vessels to right ventricle	1952	Edwards, et al.[5]
6.	7 mo.	F	—	50	3	Transposition of great vessels	1939	Harris and Farber[7] (Case 6)
7.	1 yr.	M	—	90	3	Transposition of great vessels	1939	Harris and Farber[7] (Case 12)
8.	22 mo.	—	R	—	2	Tetralogy of Fallot; accidental division of left coronary artery during ventriculotomy	1959	Kirklin[9]
9.	Child	—	R	—	1	Tetralogy of Fallot; accidental division of left coronary artery during ventriculotomy	1959	Senning[16]
10.	Child	—	L	—	1	Transposition of great vessels	1958	Keith[8]
11.	6 yr.	F	R	190	2	Tetralogy of Fallot; absent left pulmonary artery and pulmonary valve; accidental division of left coronary artery during ventriculotomy	1960	Friedman[6]

*Modification of Smith's classification (see text).

would be divided by an incision in the right ventricular outflow tract extending into the pulmonary artery. The presence of a major coronary vessel may not always be appreciated from inspection at the operating table. In such cases, temporary occlusion of the area including the upper portion of the outflow tract and the base of the pulmonary artery may indicate the presence of a major coronary vessel. In these circumstances, correction of the pulmonic stenosis might be accomplished by resection of the hypertrophied infundibulum and opening of the valve commissures, without division of the annulus.

Summary and conclusions

1. A total of 70 cases of single coronary artery have been reported, including the two new cases added in this review.

Table I.—(*Cont'd*)

Number	*Age*	*Sex*	*Single artery present*	*Weight of heart (grams)*	*Type**	*Autopsy*	*Year*	*Author*
12.	21 yr.	M	R	—	2	Myocardial ischemia after exertion	1952	Nicod[11] (Case 1)
13.	40 yr.	M	R	—	4	Thyrotoxicosis	1956	Alexander[1] (Case 2)
14.	41 yr.	F	R	460	2	Myocardial infarct	1954	Swan and Fitzpatrick[19]
15.	44 yr.	F	R	255	2	Malignant lymphoma	1939	Stapley and Edwards[18] (Case 2)
16.	49 yr.	F	R	320	1	Hemothorax, due to auto accident	1950	Dutra[3]
17.	51 yr.	M	L	—	4	SBE	1956	Alexander[1] (Case 4)
18.	56 yr.	M	L	460	2	Fatty infiltration of liver	1956	Dent and Fisher[2] (Case 2)
19.	64 yr.	M	R	—	2	Myocardial infarct	1956	Dent and Fisher[2] (Case 1)
20.	74 yr.	M	L	—	4	Myocardial infarct	1956	Alexander[1] (Case 3)
21.	77 yr.	M	L	325	1	Ca. esophagus	1939	Stapley and Edwards[18] (Case 1)
22.	77 yr.	M	R	415	2	—	1952	Nicod[11] (Case 2)
23.	79 yr.	M	L	525	1	Auricular and ventricular infarction	1959	Tremouroux, et al.[20]
24.	82 yr.	F	L	—	4	Pulmonary embolism	1956	Alexander[1] (Case 1)
25.	83 yr.	F	L	980	1	CVA; CHF	1954	Plachta and Speer[12]

*Modification of Smith's classification (see text).

2. In the majority of cases of single coronary artery the distribution of major vessels is such that a standard right ventriculotomy extending into the pulmonary artery may be made with impunity.

3. In a few cases a major vessel passes in front of the pulmonary artery. The presence of such an artery is not always apparent on inspection at the operating table, but temporary occlusion of the area of the annulus prior to division may indicate the presence of such a vessel.

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Experimental and laboratory reports

Participation of the free ventricular walls in the mechanism of production of bundle branch block

Their influence on the morphology of unipolar epicardial tracings

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The presence of conduction disturbances through the branches of the bundle of His raises numerous doubts regarding the manner in which the process of activation takes place in the heart. Much controversy and disagreement is evident in the medical literature in this respect. For some workers[1-3] the contribution of the vectorial resultant forces of the free walls in the unipolar epicardial morphologies is important. These workers relate the morphology recorded in bundle branch block (BBB) to parietal delays more than to block at the level of the interventricular septum. On the contrary, other workers[4-6,9] believe that, fundamentally, BBB morphologies are caused by the delay of the electrical impulse at the interventricular septum.

Because of this discrepancy, we decided to undertake the present study in order to assess the importance of the depolarization of the free wall of the left ventricle in cases of complete and incomplete left BBB, and the depolarization of the free wall of the right ventricle in cases of complete and incomplete right BBB.

Material and method

Forty dogs which ranged in weight between 6 and 10 kilograms were used. Pentobarbital was injected intraperitoneally at the dose of 35 mg. per kilogram. Artificial respiration was given through a tracheal cannula. The heart was exposed through a midline sternotomy. The internal mammary vessels were divided. The pericardium was cut in the midline from the diaphragmatic surface of the heart to its aortic reflection. The phrenic nerve was cut bilaterally. The divided edges of the pericardium were stretched over the lungs and sutured to the cut edges of the sternum.

Throughout the experiments the temperature of the animal was maintained at about 37°C., and blood pressure was continually recorded from the femoral artery. The electrical records were taken with a Schwarzer electroencephalograph Model 504.E with six channels. For the epicardial recordings the electrodes were small steel clamps attached to the epicardium. For the intramural and subendocardial recordings, electrodes which measured less than

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half a millimeter in diameter were mounted at different levels in a lumbar puncture needle and isolated from each other by a dielectric material.

The influence of the vectors of the free walls of the ventricles was assessed by a comparative study of the unipolar recordings from the different areas before and after the production of necrosis at different points. Necrosis was produced by the injection of chemically pure phenic acid at the sites chosen for each case.

The leads employed were: Control Lead II (L_{II}); unipolar leads to record the different morphologies of the QRS complex at different levels of the free walls of the ventricles; and bipolar leads of which the electrodes were separated 0.3 mm. from each other. These served for the study of the electrical moment of activation and the sequence of the conduction phenomenon of the electrical impulse at the different sites explored.

In order to produce BBB the technique of Wilson and associates[7] was used. The interventricular septum was tapped with a blunt needle along the path followed by the right or left branches. The electrocardiographic paper was run at a speed of 160 mm. per second to measure the propagation speed of the impulse. However, in the figures presented here, the paper speed was 60 mm. per second. Our results were uniform in 85 per cent of the experiments.

Results

In the experiment represented in Fig. 1, three sites of the free wall of the left ventricle were explored before and after the production of left BBB. Point *A* was subendocardial; *B* was intramural, with the electrode placed approximately at the same distance from *A* and *C;* and *C* was subepicardial.

Column I of Fig. 1 shows control tracing L_{II} (upper tracing) which was recorded simultaneously with the subendocardial unipolar tracing obtained at *A* (second tracing), with the intramural unipolar recording obtained at *B* (third tracing), and with the subepicardial unipolar recording obtained at *C* (lower tracing). The unipolar morphologies obtained at *A* and *B* were of the QS type, with a negative T wave and a slight degree of S-T-segment displacement, probably produced by a certain amount of injury caused by the exploring electrode. At *C* the complex was of the RS type, with a negative T wave. In Column II are the morphologies obtained at the same sites after the production of left BBB. The first two complexes in Column II show morphologies due to transient complete left BBB; then a series of transitional complexes appear which belong to lesser degrees of left BBB, which does not entirely disappear because in the last complex of this recording a different morphology from that of the control lead is readily apparent. The morphologies of the first two complexes recorded after the production of left BBB (Column II) are of the R or Rs type in points *A*, *B*, and *C*. They are simultaneous in their appearance with respect to each other and with respect to L_{II}.

As the degree of left BBB decreases, these morphologies become less and less similar. The morphology of subendocardial and intramural recordings *A* and *B* changed, i.e., a decrease in the voltage of R took place simultaneously with the appearance and gradual increase of the S wave. The morphology changed from Rs to RS and, finally, rS with a simultaneously inscribed intrinsic deflection. The subepicardial unipolar recording persisted as an R type of complex, and the inscription of its intrinsic deflection took place later than that of recordings from points *A* and *B*. As these changes appeared, the duration of the ventricular complex decreased and the T wave became less negative because of a diminution of the secondary effect after the diminution of the areas of QRS.

Fig. 2 belongs to an experiment similar to that represented in Fig. 1. Here, the free wall of the right ventricle was explored and a right BBB was produced. Three more points were explored: *A*, subendocardial; *B*, intramural, with the electrode placed 2 mm. distant from *A*; and *C*, subepicardial, with the electrode placed 2 mm. distant from *B*.

Column I of Fig. 2 shows control tracing L_{II} (upper tracing) which was recorded simultaneously with the subendocardial unipolar tracing obtained at *A* (second tracing), with the intramural unipolar tracing obtained at *B* (third tracing), and the subepicardial unipolar recording ob-

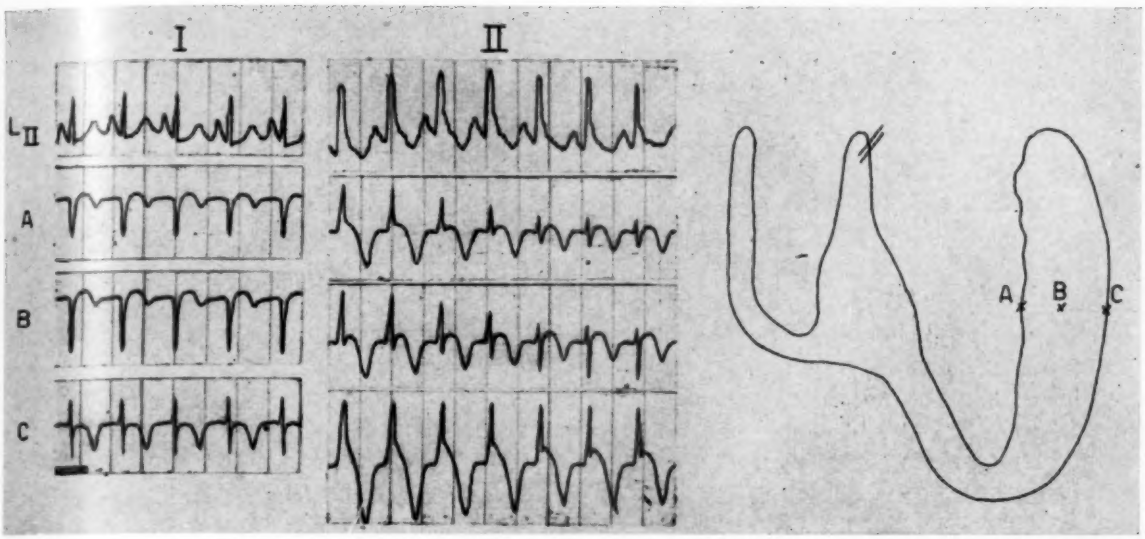

Fig. *1*. Unipolar morphologies recorded at three points of the free left ventricular wall (*A*, *B*, and *C*), obtained simultaneously with Lead II. Under normal conditions (*I*) and after the production of left BBB (*II*). See discussion in text.

tained at *C* (lower tracing). The morphologies of subendocardial unipolar tracing *A* and intramural unipolar tracing *B* were of the rS type; the positive phase of intramural tracing *B* was slightly larger than that of subendocardial unipolar tracing *A*. Subepicardial unipolar tracing *C* had an Rs morphology, and the inscription of its intrinsic deflection took place later than that of subendocardial tracing *A* and that of intramural tracing *B*. These facts suggest an activation at these levels which runs from *A* to *B* and from *B* to *C*. In Column II of Fig. 2 are tracings from the same sites after the production of right BBB; the L_{II} record (upper tracing) showed a greater duration of QRS and a wide slurred S wave. The morphologies at *A*, *B*, and *C* (second, third and fourth tracings in Column II) were of the R type and showed markedly increased slurring. Again, the morphologies of tracings from these three points suggest that the free wall of the right ventricle behaves as a volume conductor, and that its contribution to the morphologies described above is nil or very poor.

When the degree of block decreased (Column III of Fig. 2), the morphology in the L_{II} recording (upper tracing) was of the RS type, but the R was of less voltage and S was deeper than in the control tracing. This indicates that a certain degree of right BBB remained. Despite this, the morphology of the recording made at *A* became rS in type; at *B* it became RS in type, and at *C* it became only positive, i.e., of the R type. This indicates that the activation wave spreads from *A* to *B* and from *B* to *C*. In other words, again, the contribution of the free wall of the right ventricle becomes important in proportion to the decrease in the degree of right BBB.

In order to suppress the influence of the resultant vectors from the free wall of the left ventricle on the morphology of the epicardial recordings, another experiment was carried out, the results of which are shown in Fig. 3. Two subepicardial points were explored: *A*, the high portions of the lateral wall of the right ventricle, and *B*, the middle portions of the free wall of the left ventricle.

In Column I, the upper tracing is control record L_{II}; the middle tracing shows the unipolar recording obtained at *A*, and the lower tracing is the unipolar recording obtained at *B*. These tracings may be considered as control tracings. In Column II are tracings from the same sites after the production of transient left BBB. The complexes are quite characteristic of left BBB, and the morphologies in the L_{II} record (upper tracing) and in tracing *B* (lower tracing) leave no doubt as to the importance of the degree of the left BBB. The

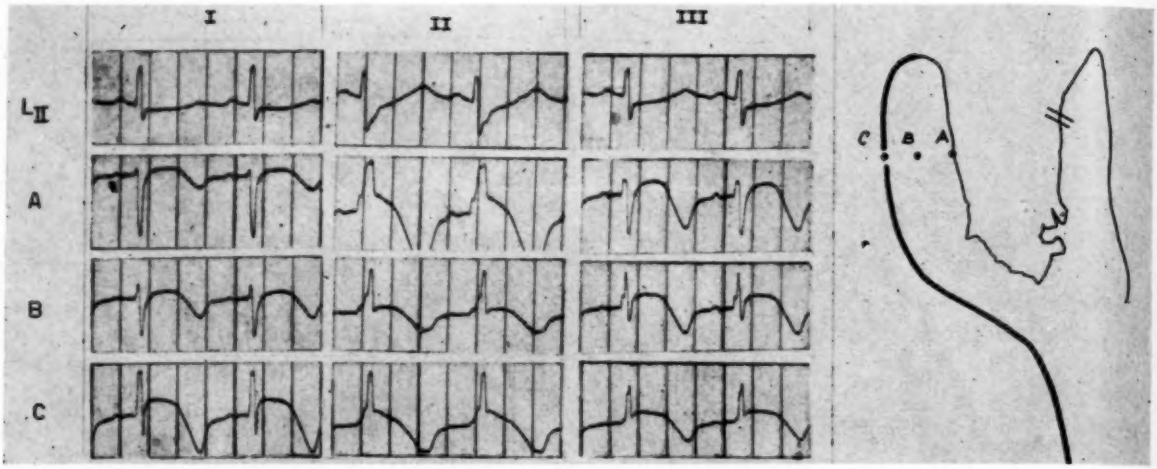

Fig. 2. Unipolar morphologies recorded at three points of the free right ventricular wall (*A*, *B*, and *C*), obtained simultaneously with Lead II. Under control conditions (*I*), with complete transient right BBB (*II*), and with incomplete right BBB (*III*).

morphology of the right subepicardial unipolar recording *A* is of the RS type, with a deep, slurred and wide S wave.

After these tracings were taken, time was allowed for the left BBB to disappear so that another control record similar to that in Column I could be made. Large and important portions of the free wall of the left ventricle, comprising 60 per cent of the free wall of this chamber, were then destroyed with phenic acid, as shown by the stippled area in the diagram in Fig. 3. Tracings taken after this destruction are seen in Column III of Fig. 3. The most important change is seen in the tracing taken at *B*, from the necrotic tissue. The complex became QS, thus indicating the importance of the necrosis. Again a left BBB was produced by percussing the bundle of His, and the same morphologies were recorded, as shown in Column IV of Fig. 3. Note that despite the large extent of destroyed tissue the morphologies of the complexes due to left BBB are like those recorded prior to the production of necrosis.

The morphology of the left subepicardial unipolar record taken at point *B* remained predominantly positive, of the R type, but was of shorter duration than that of the control tracing taken at the time of left BBB (lower tracing of Column II, Fig. 3).

We consider this experiment as quite illustrative of the slight influence of the activation of the free left ventricular wall on the morphologies of complete left BBB.

Fig. 4 shows another experiment which clarifies some aspects of cardiac activation in the presence of left BBB. Three points of the heart were explored: *A*, subepicardial, on the lateral aspect of the free wall of the left ventricle; *BB′* and *CC′*, on the interventricular septum (with close bipolar leads).

Column I shows the unipolar subepicardial tracing obtained at *A* (upper tracing) and recorded simultaneously with bipolar septal tracings obtained at *BB′* (second tracing) and *CC′* (lower tracing). The morphology of unipolar subepicardial recording *A* is of the RS type, and the bipolar tracings *BB′* and *CC′* are simultaneous, which indicates an almost simultaneous activation of these points on the septum.

Column II presents recordings from the same sites described above, after the production of transient left BBB. The morphology of the subepicardial unipolar tracing taken at *A* became predominantly positive, of the Rs type, with slurring and notching of R and an increased duration of its positive phase. The endocardial septal point *BB′* was activated 35 milliseconds before the intramural septal point *CC′*, which indicates an important conduction disorder of the left branch. The tracing taken with the intramural bipolar lead at point *CC′* showed an inversion of the greatest deflection, indicating a reversal in the sense of the propagation of the impulse.

After these tracings were made, time was allowed for the left BBB to disappear so that another control record similar to that in Column I might be made.

In Column III are recordings made with the same leads after the production of transmural necrosis of the free wall of the ventricle at the level of the site explored by the unipolar subepicardial lead *A*, as shown in the diagram. The morphology of the tracing recorded at *A* was of the QS type, as was to be expected in the case of transmural necrosis. Tracings recorded with bipolar leads at *BB'* and *CC'* continued to be simultaneous and indicated no disturbance in the conduction of the left branch. A complete transient left BBB was produced later and the tracings are shown in Column IV. The first two complexes obtained in *A* were identical with those in Column II. Under these circumstances, point *CC'* was activated 35 milliseconds after the activation of point *BB'*, thus demonstrating the same degree of left BBB as was seen in control Column II. In regard to the last two complexes of Column IV, a decrease in the time of activation between points *BB'* and *CC'* takes place. Indeed, septal point *CC'* is activated 15 milliseconds after septal point *BB'*, and the greatest deflection in the tracing from that point again becomes positive, indicating that the degree of left BBB decreases significantly. The morphology of the unipolar subepicardial tracing from *A* changed from Rs to rS. Since the electrode exploring point *A* recorded the variations in intracavitary potential once the vectorial forces of the free wall of the left ventricle had been eliminated by means of necrosis, it was to be expected that the changes taking place in the positive deflection of the recording obtained at *A* originated in the variations in potential of the interventricu-

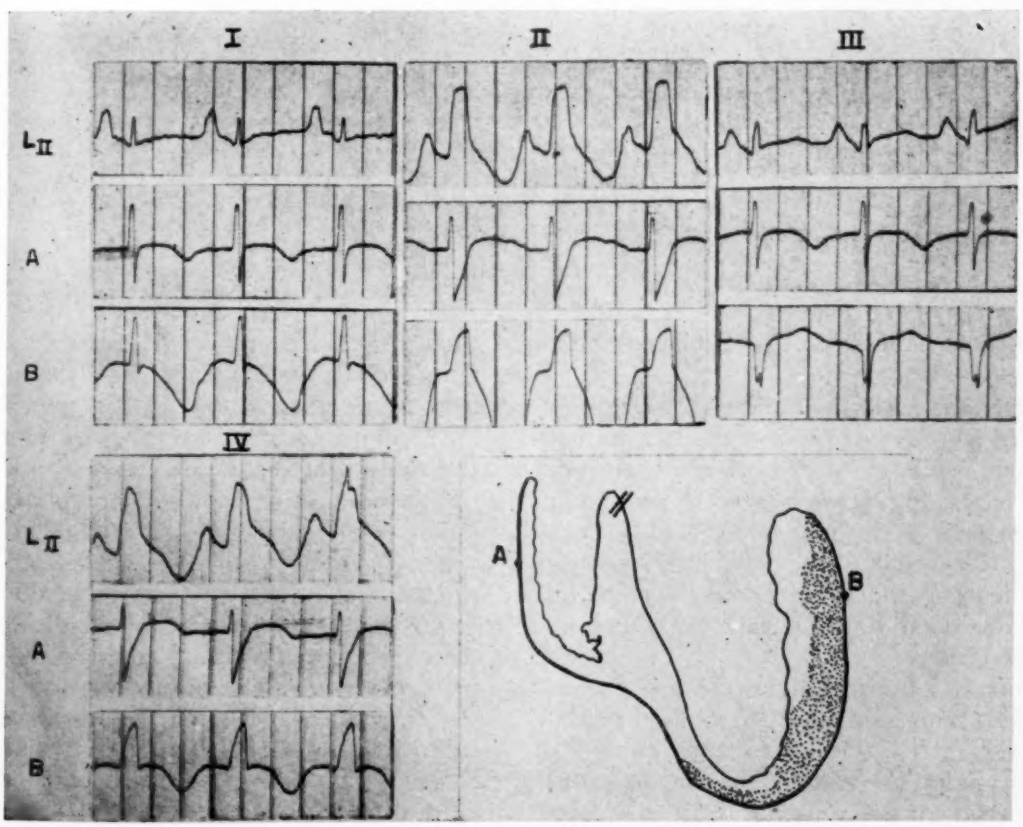

Fig. 3. Lead II with simultaneous recordings from two epicardial points: one in the free wall of the right ventricle (*A*) and the other in the free wall of the left ventricle (*B*). Under control conditions (*I*); after the production of transient left BBB (*II*); with necrosis of the free wall of the left ventricle, as shown in the diagram, and without conduction disturbances of the left bundle branch (*III*); with parietal necrosis and complete left BBB (*IV*).

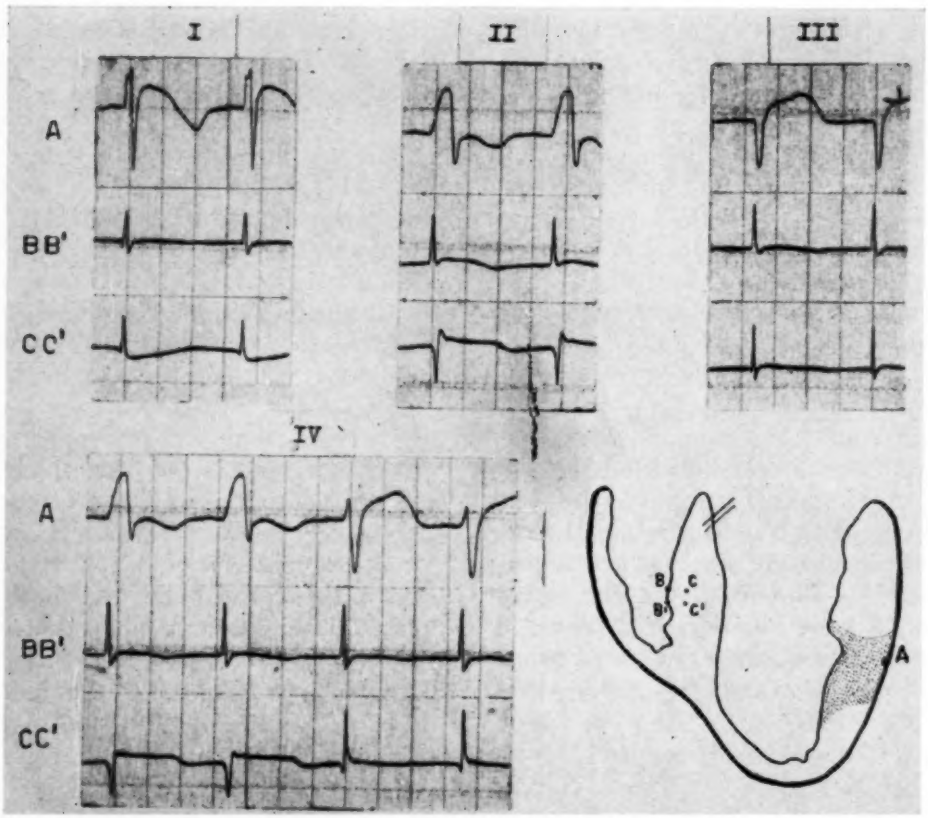

Fig. 4. Unipolar epicardial lead records obtained from the free wall of the left ventricle (*A*), simultaneously with proximal bipolar lead tracings from the right endocardial surface (*BB'*) and from the thickness of the septal mass (*CC'*). Under control conditions (*I*); with transient complete left BBB (*II*); with transmural necrosis of the free wall of the left ventricle and without conduction disturbances of the branch (*III*); with transmural necrosis of the free wall of the left ventricle and with complete block of the left bundle branch (*IV*).

lar septum, which is a direct function of the degree of block.

Fig. 5 illustrates the findings in an experiment in which two points of the free wall of the right ventricle were explored with unipolar leads. *A* corresponds to the unipolar lead exploring the subendocardial surface at the trabecular zone, and *B*, to the unipolar lead at the subepicardial surface on the same lead line as unipolar subendocardial lead *A*.

Control Column I shows the L_{II} record (upper tracing) which was recorded simultaneously with the tracings of subendocardial unipolar lead *A* (second tracing) and subepicardial unipolar lead *B* (lower tracing). It is apparent that unipolar subendocardial tracing *A* shows an rS morphology, whereas in tracing *B* the rS morphology persists although R is of greater voltage than that seen in *A*. This fact indicates that the greater voltage of R in the unipolar tracing *B* is given by the activation of the muscular mass between *A* and *B*. Column II shows recordings made in the same previously described leads, after the production of transient complete right BBB. Under these circumstances, L_{II} became type RS, with notchings and slurrings of the S wave and a greater duration of QRS than under control conditions, as seen in Column I. These changes show the importance of the conduction disorder of the right bundle branch. The tracings obtained with unipolar subendocardial lead *A* (second tracing) and unipolar subepicardial lead *B* (lower tracing) show predominantly positive morphologies of the R type, with a duration of the QRS greater than that of the control recording. The initial parts of these two morphologies are simultaneous.

Once the right BBB had disappeared and the electrocardiographic recording returned to control conditions, as in Column I, a transmural necrosis of the free wall of the right ventricle was produced at the sites explored, *A* and *B*, as shown in the diagram. The results are shown in Column III, where it may be seen that the unipolar recordings from points *A* and *B* became similar, i.e., the high R wave in the tracing made at point *B* disappears. This fact shows that the R wave recorded by the subepicardial lead *B* was due to the activation of the underlying muscular mass at point *B*.

The tracings of Column IV were recorded after the production of transmural necrosis of the free right ventricular wall and complete right BBB. The morphologies of the L_{II} record (upper tracing) are similar to those in Column II, a fact which indicates that there is a certain degree of right BBB similar to that registered as a control or a reference in the same Column II. The unipolar subendocardial recording *A* and subepicardial *B* show predominantly positive morphologies of the R type, with duration of QRS greater than that seen in Columns I and III, and with a simultaneous initial deflection. It may also be seen that the morphologies of the unipolar recordings obtained at *A* and *B* under these circumstances are very similar to those of control tracings in Column II.

The experiment illustrated in Fig. 6 was similar to the one described in Fig. 5, except that this time the free wall of the left ventricle was explored. Two points of the middle portion of the lateral aspect of the wall were explored with unipolar leads: *A*, subendocardial; and *B*, subepicardial at the same level as *A*.

Column I shows the L_{II} record (upper tracing) which was recorded simultaneously

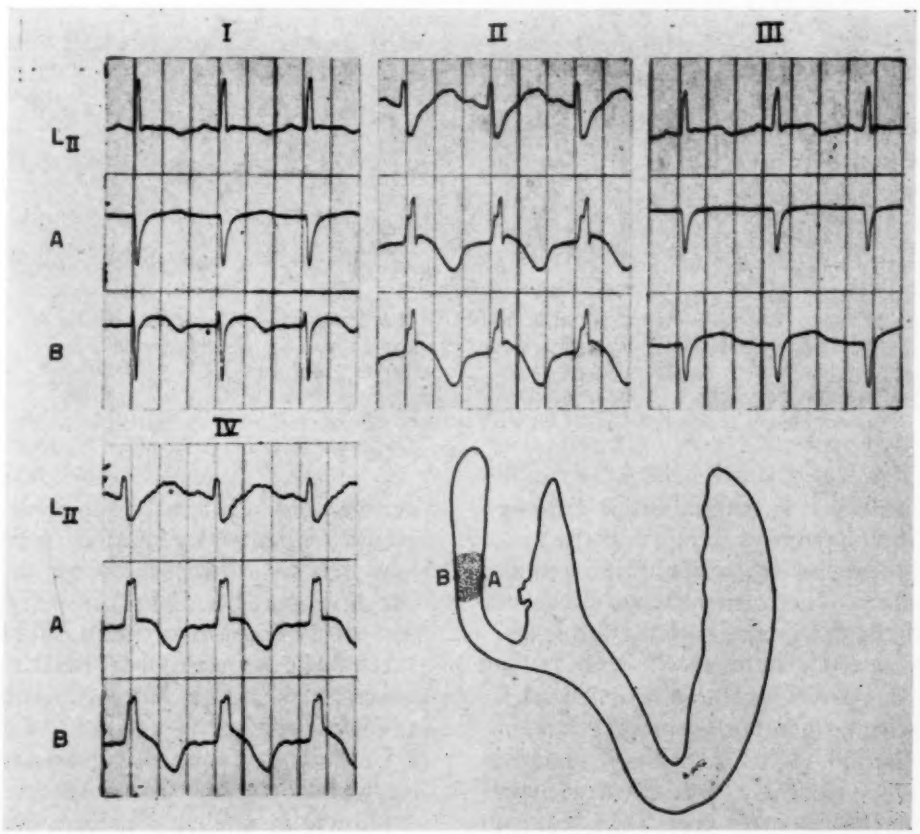

Fig. 5. Lead II recorded simultaneously with unipolar morphologies from two points in the free wall of the right ventricle: *A*, subendocardium, and *B*, subepicardium at the same level as *A*. Under control conditions (*I*); with complete transient right BBB (*II*); with transmural necrosis, as shown in the diagram, and without conduction disturbance of the branches (*III*); with transmural necrosis and complete right BBB (*IV*).

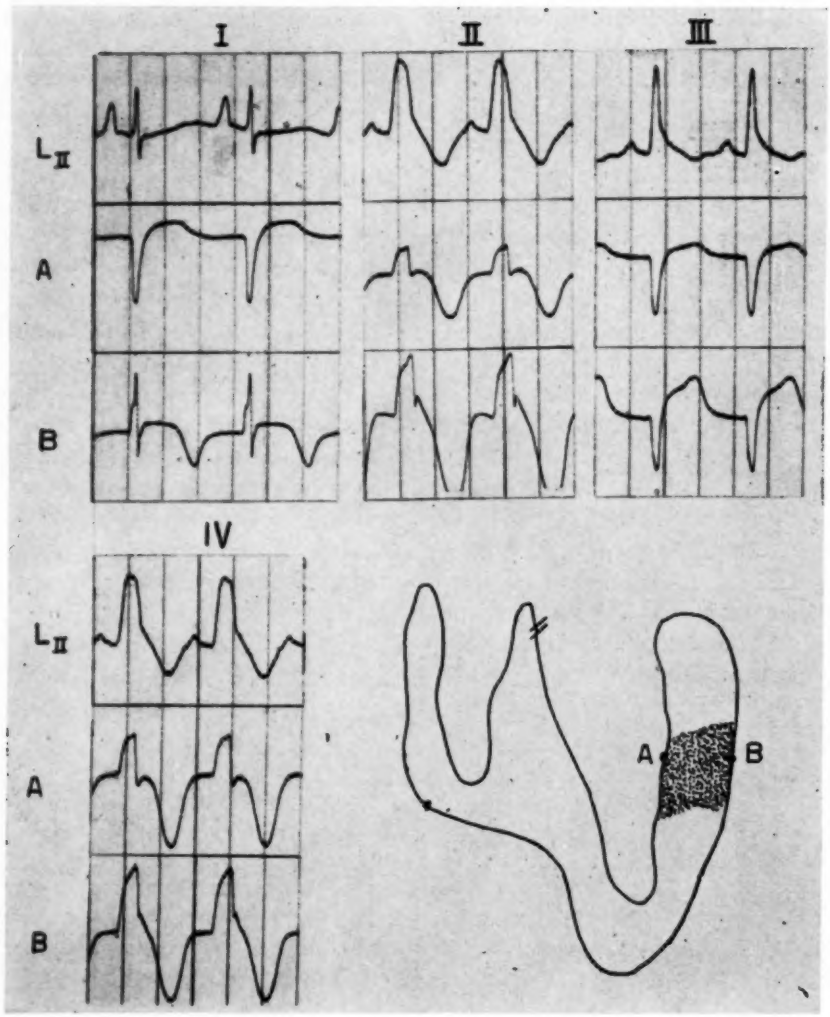

Fig. *6*. Lead II recorded simultaneously with tracings from two points in the free wall of the left ventricle: *A*, subendocardium, and *B*, subepicardium. Under control conditions (*I*); with complete transient left BBB (*II*); with transmural necrosis of the free wall of the left ventricle and without conduction disturbances of the branch (*III*); with transmural necrosis and left BBB (*IV*).

with the unipolar subendocardial tracing obtained at *A* (second tracing) and the unipolar subepicardial tracing obtained at *B* (lower tracing). The former shows QS complexes and the latter shows RS complexes. These are control tracings.

Column II shows tracings recorded with the same leads after the production of transient complete left BBB. The L_{II} record became predominantly positive, with a duration of QRS greater than that seen in control Column I, and with notching and slurring of R, a fact which denotes the importance of the degree of left BBB. The tracings obtained with unipolar subendocardial lead *A* and subepicardial lead *B* became predominantly positive, of the R type, with a duration of QRS greater than that seen in control Column I. These morphologies (L_{II}, *A* and *B*) may be taken as control or reference tracings for left BBB.

After the transient left BBB had disappeared and the electrocardiographic tracings had returned to the control conditions of Column I, a transmural necrosis of the free wall of the left ventricle was produced as shown in the figure. This necrosis involved the muscular mass explored by the electrodes at points *A* and *B*. Column III shows the tracings recorded. Subendocardial unipolar morphologies (second tracing) were still of the QS type like those of

control Column I. The unipolar subepicardial morphologies were also of the QS type, and this would seem to be due to the destruction of the muscular masses responsible for the vectorial forces which gave the R wave of the subepicardial recording.

The tracings of Column IV were recorded after transmural necrosis of the free left ventricular wall and complete left BBB had been produced. The L_{II} record (upper tracing) shows the same features described in the control tracing of Column II. The unipolar subendocardial recording *A* and the subepicardial unipolar recording *B* show morphologies with characteristics very similar to those obtained in the control tracings of Column II (second and third tracings); that is, they became predominantly positive, with duration of QRS greater than in the control lead, with notchings and slurrings of R.

Discussion

The use of a method which eliminates muscular areas of the ventricular walls, with consequent elimination of the vectorial forces of these areas, permitted us to study the influence of these vectorial forces on the unipolar morphologies recorded at different levels of the free wall of the ventricles and with different degrees of BBB.

That the vectorial forces of the free wall of the ventricles present in the control tracings had been eliminated became evident in the disappearance of the epicardial deflection after the production of necrosis of the explored areas.

Our experiments show that, when there is a complete BBB, the morphologies of the unipolar recordings obtained in the entire thickness of the free wall on the same side as that in which the block exists are produced fundamentally by potentials originated at the level of the interventricular septum, a fact which was proved initially by Medrano and associates[5] and later by Anselmi and associates.[6] In fact, the simultaneously inscribed records of the points explored in the subendocardial, intramural, and subepicardial portions of the free wall of the blocked side speak in favor of the view that the vectorial forces which give rise to these morphologies originate at points other than in the free wall of the ventricle. This is proved by the persistence of the morphologies of the unipolar recordings after elimination, by means of the parietal necrosis, of the vectorial forces originating in the free wall of the ventricle. The free walls of the ventricles behave as conductors in the presence of complete BBB, and the vectors originated through their activation have slight influence on the morphologies of the unipolar recordings obtained at different levels.

Our experiments afford evidence contrary to the view held by those who attribute the unipolar morphologies of BBB to delays of the impulse at the level of the free walls of the ventricles.[1] In fact, if the impulse suffered any delay in the speed of propagation at the level of the muscular mass of the free walls of the ventricles, one should expect an alteration in their morphology once the muscular mass was destroyed. But this was not seen in any of our experiments. Likewise, we cannot admit the explanation proposed by some workers,[2] according to whom the activation of the free wall in the case of BBB progresses from the apex to the base of the heart, with a front wave which is perpendicular to the endocardial and epicardial surfaces. If this were true, once the wave of activation passed the explored points of the free wall to ascend to the basal portions, it would produce an important negative wave at those points, giving rise to RS complexes instead of R or Rs morphologies as were obtained in our experiments. On the other hand, if these morphologies had their origin in the same free walls, a modification in the recordings should be expected once the muscular masses giving rise to them had been destroyed. Again, this was never seen in our experiments.

By application of the concept of "electrical window,"[8] the variations in potential recorded at the epicardium of a necrosed portion should be attributed to the variations in potential of the ventricular cavity toward which the exploring electrode is oriented. For this reason the progressive decrease in the positive deflection which takes place in the unipolar recording obtained at the epicardium of the necrosed area as the block decreases must be attributed to a decrease in the vectorial forces

originated at the interventricular septum. The variations of the septal potential are directly proportional to the degree of BBB. As the septal vectorial forces decrease as a result of a lesser degree of BBB, their influence on the epicardial unipolar recording becomes shorter and less important. Under these circumstances the vectors which result from the activation of the free wall of the ventricles manifest themselves, adding their action to the septal resultants. This causes the unipolar epicardial recordings to be influenced by these two vectorial forces: septal and free wall. The unipolar morphology obtained at the epicardium of the side homologous to the block does not show significant changes when the block is complete or when this block decreases. In the first case, the morphologies are primarily conditioned by differences in septal potential, whereas in the case of a lesser block, both factors contribute: (1) the septal vectorial resultants whose influence is directly related to the degree of block, and (2) the vectorial forces originating in the free wall of the ventricle, of later appearance than those of the interventricular septum.

From a practical standpoint it is difficult to determine when a given morphology corresponds to a complete block and when to an incomplete block, since, at the present time, the information supplied by the electrocardiogram makes it impossible to assess the participation of each component.

Summary

A study has been made of the influence of the vectorial resultants of the interventricular septum and those of the free walls of the ventricles on the unipolar recordings at different levels of the free wall of the ventricles with different degrees of bundle branch block (BBB).

The influence of the vectorial resultants of the free walls of the ventricles was assessed by a comparative study of the unipolar morphologies recorded at different points of the wall before and after the production of parietal necrosis at the same point the lead.

The importance of the vectorial forces of the interventricular septum on the unipolar morphologies of BBB becomes apparent when the block is complete. Our evidence indicates that the vectorial forces of the ventricular septum are directly related to the degree of block, and that, when the resultant vectorial forces of the ventricular septum decrease because of a diminution in the degree of BBB, the vectorial forces of the free wall of the ventricle on the side homologous to the block become manifest.

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Clinical estimation of the volumes of blood in the right heart, left heart, and lungs by use of I^{131} albumin

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After I^{131}-labeled human serum albumin has been injected intravenously, the radioactivity of an organ parallels its plasma content until a significant amount of the I^{131} has escaped from the vascular compartment. If the total radioactivity of an organ or region could be measured accurately in vivo, its plasma content could be determined by comparing the radioactivity per unit volume of plasma with the activity of the whole organ. In the case of the heart, most of the observed radioactivity would be derived from plasma within the cardiac chambers, rather than the coronary vessels. By application of the principles developed for the analysis of the dilution of dye in flowing blood,[1,2] it would be possible to estimate the volumes of blood in the right heart and the left heart and in the lungs. The present study was done to test the principles and define some of the problems of such measurements.

Materials and methods

Subjects. Fifteen hospitalized subjects with no evidence of heart disease were compared with 26 patients under treatment for cardiovascular disease. The diagnoses in the latter group were: essential hypertension, 8; arteriosclerotic heart disease, 2; myocarditis of unknown etiology, 2; massive pericardial effusion due to carcinoma and to lupus erythematosus, 1 each; thyrotoxic heart disease, 1; syphilitic heart disease, 1; rheumatic heart disease involving mitral and aortic valves, 2; rheumatic aortic stenosis with insufficiency, 2; and rheumatic mitral stenosis, 6.

Placement of the counter. Each subject was fluoroscoped in the supine position, and the surface projections of four locations were indicated on the anterior chest wall. These were the cardiophrenic angles and two points on the opposite borders of the cardiac shadow immediately below the pulmonary artery. A four-sided cardboard pattern was constructed with dimensions based on these points. This was used to guide in the placement of lead shielding, so that the center of the crystal, the inner edge of the shielding placed over the chest wall, and the border of the cardiac shadow would fall along a straight line. With this arrangement all of the scintillation crystal could be "seen" from any point within the heart, and, at the same time, as much tissue to either side of the heart as possible

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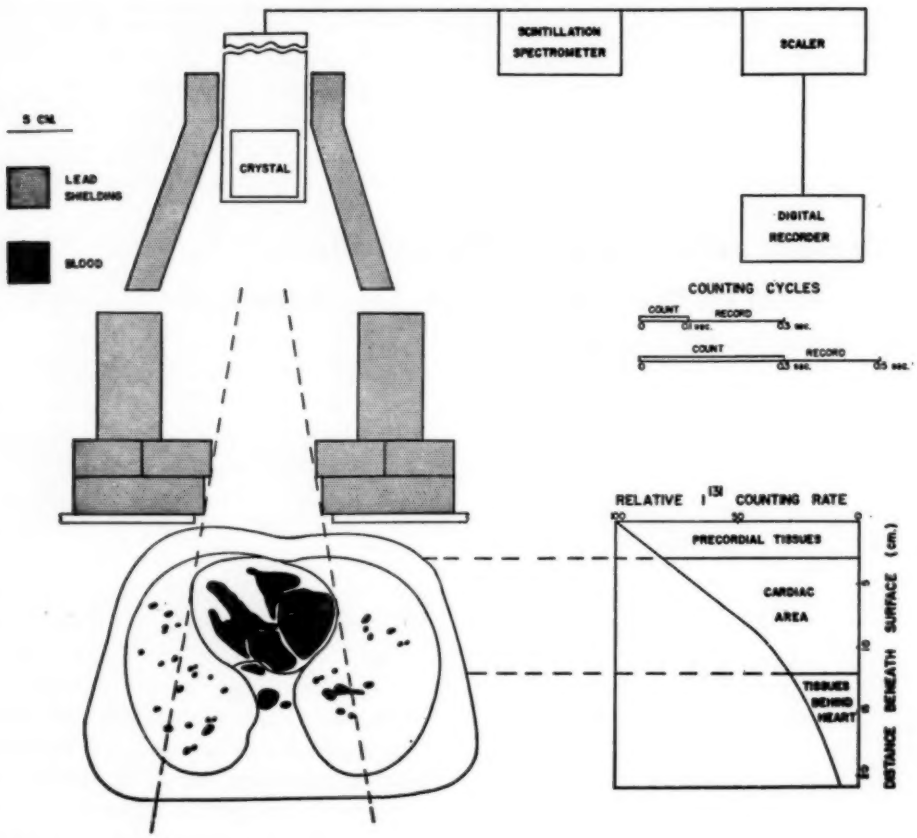

Fig. *1*. The arrangement of apparatus for determining radioactivity of the cardiac region after intravenous injection of I^{131} albumin. The relative counting rate of an I^{131} source at varying depths in a masonite phantom is shown.

was eliminated (Fig. 1). The heavily shielded 2-inch by 2-inch cylindrical NaI crystal was positioned over the center of the heart, 25 cm. from the anterior chest wall. The scintillation pulses corresponding to energies below 0.15 Mev. were eliminated by a spectrometer, and the remainder were recorded automatically every 0.3 to 0.5 second by a Hewlett-Packard 560-A digital recorder.

Injection of I^{131} albumin. One hundred microcuries of radioiodinated human serum albumin (Albumotope, Squibb) was injected into a medial antecubital vein and was followed by a flush of 5-10 ml. of 0.8 per cent NaCl solution. The injection time ranged from one to several seconds. The activity of the I^{131} albumin solution was determined in a weighed dilution employing a 1 per cent aqueous detergent solution (Alconox)[3] and assayed with Geiger-Müller tubes.[4] The quantity injected was equal to the amount placed in the syringe, determined gravimetrically, less that which could be recovered in washings from the syringe and needle after the injection. In 9 lots of labeled albumin, 3.0 ± 0.9 per cent of the radioactivity was not precipitated by addition of saturated ammonium sulfate and centrifugation at 20,000 RCF. No correction for this apparently "unbound" activity was made.[5]

Measurements after isotope injection. Radioactivity of the cardiac area was recorded for 10 minutes. Blood was then collected from a second vein into a tube containing dry heparin, and the hematocrit was determined by centrifugation for 45 minutes at 2,000 RCF, correcting for 3 per cent trapped plasma.

Calculations

Plasma volume. The observed dilution of the total amount of labeled albumin was used for calculating total plasma volume, assuming that complete mixing and no loss of tracer from the blood had occurred 10 minutes after the injection.

Blood volume. The total blood volume was estimated from the plasma volume and the venous hematocrit. No allowance was made for a lower total body hematocrit.

Total intracardiac blood volume. By comparison of the activity over the precordium 10 minutes after injection of the isotope with that of the peripheral venous blood at the same time, the total intracardiac blood volume was estimated. An I^{131} albumin source of known strength was counted, under the conditions employed for the subjects, at increasing depths within a phantom of masonite, a fiberboard with density approximating that of tissue (Fig. 1). The mean counting rate of 1 microcurie of I^{131} within the zone occupied by the average normal heart was calculated and related to the counting rate per microcurie of I^{131} observed with the Geiger-Müller tube employed in all studies. With the particular instruments and techniques employed, 1 μc of I^{131} produced 265,000 cpm. with Geiger-Müller counting, and 1,600 cpm. when evenly distributed along the anterior-posterior axis of the cardiac area. Therefore, for these particular counters, intracardiac blood volume in milliliters was estimated from:

$$\frac{\text{Precordial radioactivity (cpm.)}}{\text{Whole blood radioactivity (cpm./ml.)}} \times 166 \qquad (1)$$

Both counters were standardized with known sources before each use, but no corrections for changes in counter sensitivity were made since only minor variations occurred.

Right- and left-sided components of the intracardiac blood volume. A semilogarithmic plot was made from the digital record of radioactivity of the cardiac region (Fig. 2). In all but 4 instances these graphs demonstrated 2 peaks during the first circulation of the isotope through the heart and lungs, corresponding approximately to the periods of maximal concentration of isotope in the right and left sides of the heart. Curves *a*, *b*, and *c* in Fig. 2 are representative of measurements in 23 subjects in whom it was believed possible to make a meaningful linear extrapolation of the decline of radioactivity in the right heart. The lowest concentration observed between the peaks in these subjects averaged 0.51 ± 0.10 times the peak concentration in the right heart. In Fig. 2, curve *a* is a typical result; *b* is one in which the right-sided component is unusually well defined; and *c* is of borderline quality for extrapolation. The left-sided component was obtained by subtraction, and similarly extrapolated on the assumption that this decline also was linear with time. Curve *d* was obtained from a subject with a large heart and low cardiac output. It is clearly unsatisfactory for attempting such a division. There were 10 such instances. In the study represented by curve *e* of Fig. 2 there was a bifid right ventricular component, presumably caused by irregular outflow of the isotope from the arm. There were 5 such curves. In 2 subjects the apparent slope of the left-sided curve was steeper than the right (Fig. 2,*f*). This was thought to represent inaccurate extrapolation of the right component, or a changing rate of blood flow. In one subject the injection was incomplete. In these studies no calculations based on separation of the two sides were made.

The portion of the total intracardiac blood volume contained in each side of the heart was estimated from the relative areas of the right and left components of the curves of precordial radioactivity. The rationale of this calculation was as follows. The precordial radioactivity at any time during the first passage of the isotope was assumed to be proportional to the total amount of isotope within the combined right and left sides of the heart at that instant. Since the mean volumes of the two sides do not change significantly during this period, the height of the right and left components of the curve were proportional not only to the total amount, but also to the average concentration of isotope within each of these segments at any instant throughout the period of the first passage of the isotope. However, since the amount of blood on the two sides is not equal, the heights of the two curves do not indicate the relative concentrations per milliliter of blood on the two sides. In each cardiac chamber:

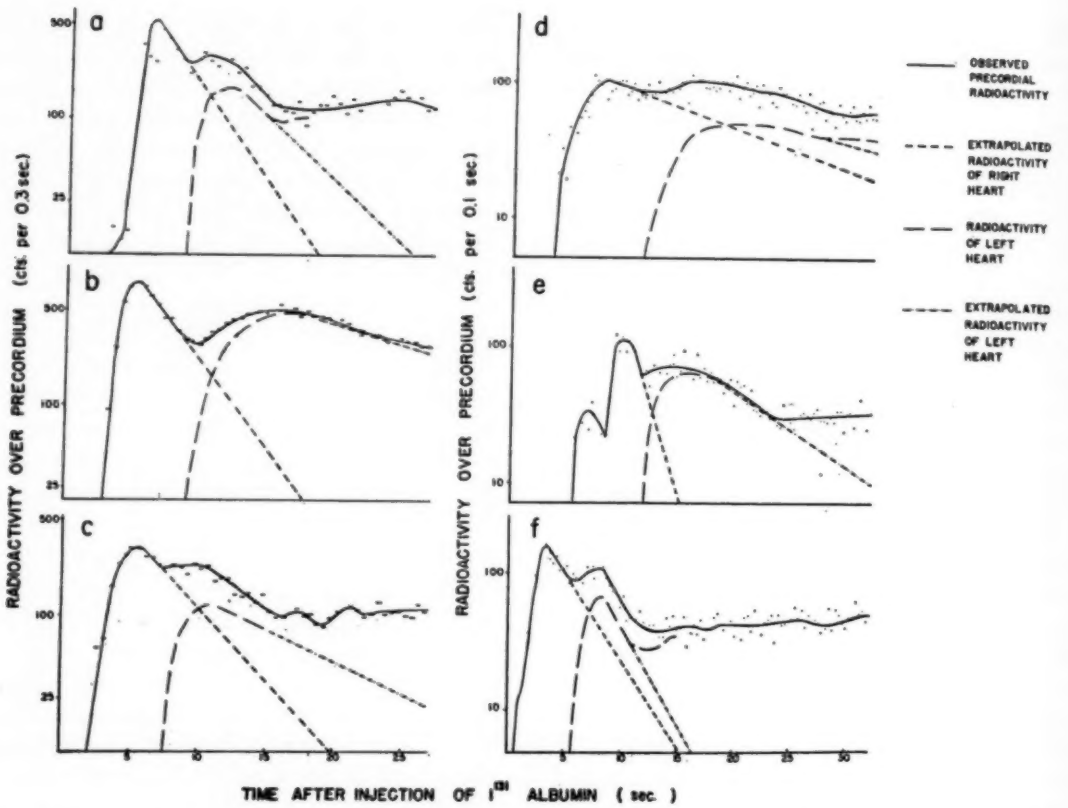

Fig. 2. Precordial radioactivity after the intravenous injection of I^{131} albumin in 6 subjects. Radioactivity is shown on a logarithmic scale. Curves *a*, *b*, and *c* were satisfactorily divided into right and left heart components, whereas in *d*, *e*, and *f* this was not possible.

$$I = F \times T \times A \qquad (2)$$

where I is the quantity of isotope passing during the first circulation, F is the volume of blood flow per unit time, T is the time required for the initial passage of the bolus of tagged blood, and A is the average concentration of tracer in the blood during the initial passage. But:

$$A = \frac{Ac}{T} \times K$$

where Ac is area under the concentration-time course curve during the first circulation, and K is a proportionality constant. Therefore:

$$I = F \times Ac \times K$$

or

$$Ac = \frac{I}{KF}$$

Since $\frac{I}{KF}$ in the right and left sides of the heart is equal, Ac is also equal in the two sides.

When the monitor is recording equally from equal volumes of blood in the right and left sides of a heart without a shunt, the areas of the right and left precordial curves are necessarily equal. The actual observed areas of these curves must be proportional to the volumes of blood effectively monitored. The remote placement of the crystal and the arrangement of precordial shielding so that all of the heart would be "seen" by the monitor was intended to provide equal geometric representation of all blood within the heart.

Pulmonary blood volume. The mean circulation time from right heart to left heart was calculated arithmetically from the concentrations at one-half-second intervals[2] in those measurements in which right and left components were separated. The volume of blood between the right and left sides is defined by this mean circulation time and the cardiac output. It is clear that this volume as measured in these subjects includes a portion of the intracardiac volume. As an aid in finding a

useful correction for this intracardiac contribution, a simple model was used which is outlined in Fig. 3. Results obtained with this model are given in Table I. When one half of the intracardiac volume was subtracted from the total, an accurate result for "pulmonary" volume was obtained. This correction was also applied to the data from man.

Cardiac output. Cardiac output (F) was calculated by the method of Huff and associates[6,7] and Veall and associates,[8] making use of the average concentration within the right and left hearts combined during the first passage of isotope (A′), the time required for the first passage (T′), the concentration in the blood after complete mixing of the isotope at 10 minutes (C), and the blood volume (BV).

$$F = \frac{(C) \times (BV)}{(A') \times (T')} \qquad (3)$$

Results and interpretation

Intracardiac blood volume. Intracardiac blood volume ranged from 370 to 2,100 ml., averaging 345 ± 55 ml./M.² or 614 ml. total, in 16 subjects without evidence of heart disease. The relation of these estimates to the approximate size of the precordial projection of the heart is shown in Fig. 4. In both of the subjects with known pericardial effusion, there was approximately 500 ml. less intracardiac blood than would have been expected from the size of the heart shadow. This large variation from the mean relationship is probably caused by the effusion, which enlarges the cardiac shadow and partially shields the intracardiac blood from the counter. In the group of 21 determinations in which the size of the heart shadow of those with and without heart disease overlapped, there was less intracardiac blood for a given size of heart shadow in those with heart disease ($p = 0.04$). The presence of ventricular hypertrophy in the latter group seems to be the most obvious explanation for this difference which is shown more clearly in Fig. 5. The 11 subjects with heart disease suffered from hypertension or rheumatic valvular deformity. Myocardial hypertrophy was prominent clinically in this group, but dilatation was minimal.

Blood content of the right and left sides of the heart. The partition of intracardiac volume was estimated in 23 subjects. In those without heart disease the volume of the right heart averaged 170 ± 25 ml./M.², and that of the left heart, 185 ± 50 ml./M.². The average body surface area of this group was 1.82 M.². Fig. 6 shows the division of the intracardiac blood. This did not correlate well with the side of the predominant ventricular dilatation as judged from clinical data. Atrial blood is included in the volume measured, and bilateral enlargement of the heart was present in many instances.

Pulmonary blood volume. In 9 subjects without heart disease, pulmonary blood volume was 490 ± 130 ml./M.², or 16.5 ±

Table I. *Results of all determinations of the volume of the "pulmonary" component of a vascular model**

Number	*Rate of flow (ml./min.)*	*Mean circulation time, right to left (sec.)*	*Calculated "pulmonary" volume (ml.)*	*Sum of actual "pulmonary" volume and one half of chamber volume (ml.)*	*Actual "pulmonary" volume (ml.)*	*Combined chamber volume (ml.)*
1a	461	16.2	124.5	123.0	65.1	115.7
2a	218	33.6	122.1	123.0	65.1	115.7
3a	343	21.7	124.1	123.0	65.1	115.7
1b	279	20.5	95.3	96.3	38.4	115.7
2b	208	30.6	106.1	96.3	38.4	115.7
3b	244	23.8	96.8	96.3	38.4	115.7

*Dye dilution principles were applied to the analysis of external monitoring of the flow of a bolus of radioactive material through the model. Rates of flow and pulmonary volume were varied. Calculated "pulmonary" volume closely approximated the sum of the actual "pulmonary" volume and one half of the chamber volume.

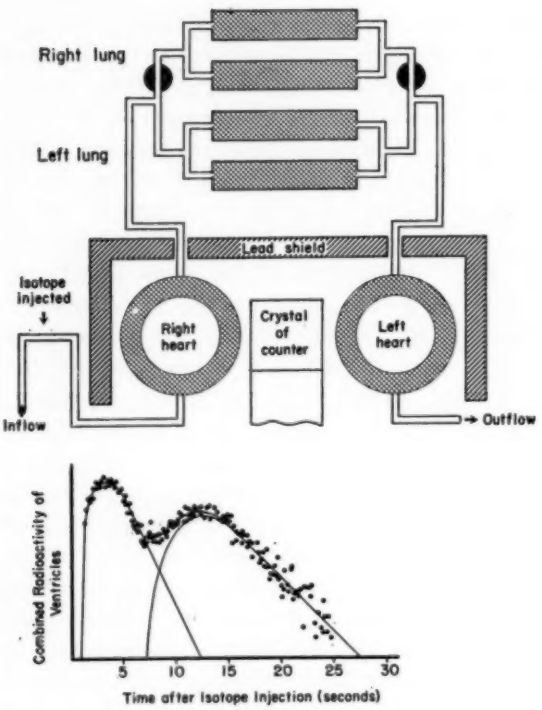

Fig. 3. Model demonstrating pulmonary blood volume determination. The chambers are partly filled with glass beads to insure mixing of isotope and water. The scintillation counter is shielded from radiation originating in the "lungs." One curve obtained is illustrated.

3.7 per cent of the total blood volume. The results were essentially the same in patients with heart disease, including those with mitral stenosis (Fig. 7). The degree of variation was marked.

Discussion

Measurement of intracardiac volume. The inability to obtain adequate depth focus with scintillation detectors presently in use is a major limitation in most isotope techniques making use of in vivo monitoring. The anterior chest wall, the myocardium, the pulmonary vessels adjacent to the heart, and the structures of the posterior mediastinum, spine, and posterior chest wall all contain blood that is within the field of the counter as employed in these studies. The combined effective volume of these tissues is probably small compared to the intracardiac volume, partly because of the absorption of radiation from the deeper structures. This decrease in effective counting rates at increasing depths is one of the sources of error which makes the use of a single calibration factor for all hearts necessarily erroneous. The marked differences observed in the 2 subjects with pericardial effusion are encouraging and suggest a diagnostic application of this technique. The method in its present form appears to be sensitive to the presence of myocardial hypertrophy. This suggests that the variations in extracardiac contributions to the measured volume, and in the factors affecting the true calibration for external counting, may not be so great as might be supposed. The major error in the division of the total volume between right and left sides probably arises in the extrapolation of the observed data. The somewhat more posterior position of the left ventricle and the added shielding from its thicker wall may lower the counting rate from the blood within the left side of the heart somewhat. Sutton and co-workers[9] have shown that red cells injected into the pulmonary artery of man begin to appear in the right ventricle in 7 to 9 seconds. Therefore, significant recirculation of isotope into the right heart probably occurs early on the downslope of the curve of the left side of the heart. This may be a significant source of error in the extrapolation of this component.

Prinzmetal and co-workers[10] suggested the use of "radiocardiography" to distinguish myocardial hypertrophy from chamber dilatation, and Shipley and his associates[11] noted that the area under the right or left component was correlated with the volume of the chambers. They believed that the detection of enlargement of the combined atrial and ventricular chambers might be possible, although no such study was reported. Similar suggestions have been made by Huff and associates.[12]

The intracardiac blood volume can be estimated from the difference between the total heart volume as calculated radiologically from the heart shadow in vivo and the volume of the cardiac muscle at postmortem examination. From radiographic studies, Liljestrand and associates[13] have obtained mean values for the total volume of the living heart ranging from 700 to 750 ml. Since the volume of the normal heart muscle as estimated from its weight is approximately 260 ml.,[14] the normal total intracardiac blood volume as judged by this method is in the range of 440 to

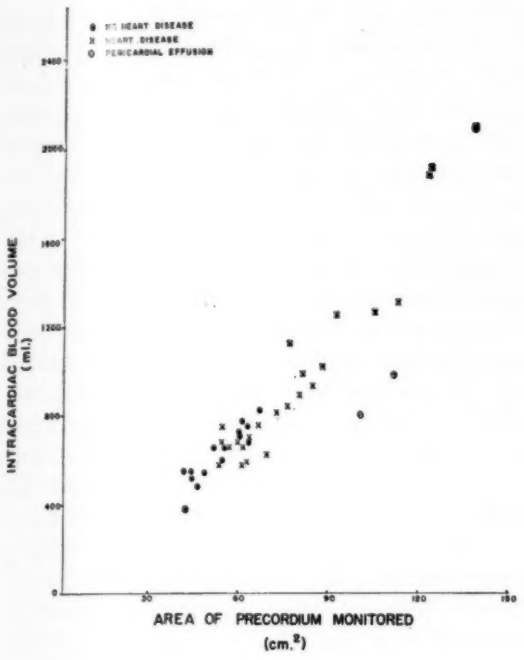

Fig. 4. Relation of intracardiac blood volume in 41 subjects with and without heart disease to the size of the heart shadow. The heart size is indicated by the area of precordium monitored during the determination of cardiac radioactivity.

490 ml. The average in the present isotope study was 614 ml. total volume. Another approach is to measure the amount of liquid required to fill the cardiac chambers at autopsy. Velazquez[15] obtained total volumes of from 108 to 298 ml. in 12 normal hearts filled with a paraffin mixture. Soloff and Zatuchni[16] have introduced a method of calculating the volumes of the four chambers by means of simultaneous biplane stereoscopic angiocardiograms. They studied 18 patients with mitral stenosis and found an average 887 ml. (range, 595-1, 341 ml.) for the total capacity. The average volume in 6 subjects with mitral stenosis in the present group was 692 ml. The fractional discharge rate of dye or I^{131} albumin from the intracardiac cavities has been used as the basis for estimates of ventricular volume,[17-21] but the errors inherent in these methods have not as yet been adequately defined.

Pulmonary blood volume. The errors which affect the separation of the right and left curves for the partitioning of intracardiac volume are also involved in the calculation of the mean pulmonary circulation time, upon which estimation of the pulmonary blood volume depends. The basic validity of the dye-dilution method for the determination of cardiac output has been extensively discussed in the recent literature,[22-24] and the related techniques employing injection of isotopes and external monitoring have been well described.[6-8] The particular method of estimating cardiac output used in the present study does not differ greatly from those employed by others in work which has demonstrated the accuracy of this approach.[25] Technical problems have been considered in detail by MacIntyre, Pritchard, and Moir.[26,27] These authors have suggested that the absence of an increase in precordial radioactivity after the first circulation was one indication that the equilibrium observation was made on the same volume of blood monitored during the initial circulation. In the present group of determinations the precordial radioactivity immediately after the left ventricular downslope averaged 1.12 ± 0.14 times the concentration at 10 minutes. It is possible that the particular correction for the volume of blood within the heart in the present technique may have a sound theoretical basis, provided that adequate mixing and equal geometric representation of the two sides of the heart to the counter are achieved. It has been repeatedly pointed out that only actively circulating blood is measured by the dye-

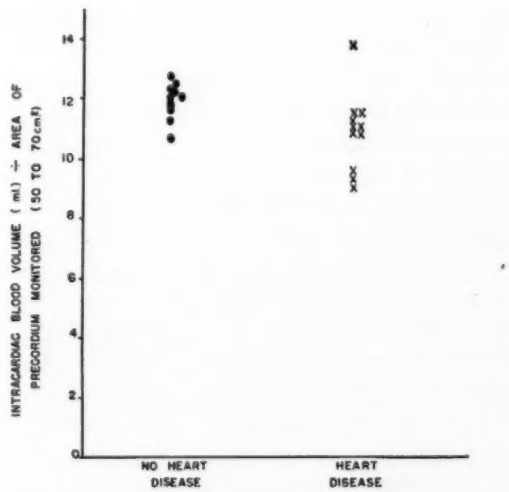

Fig. 5. Comparison of the ratio of intracardiac blood volume to the area of the heart shadow in a group of subjects with normal hearts and in a group with heart disease. The sizes of the heart shadows were in the same range for the two groups.

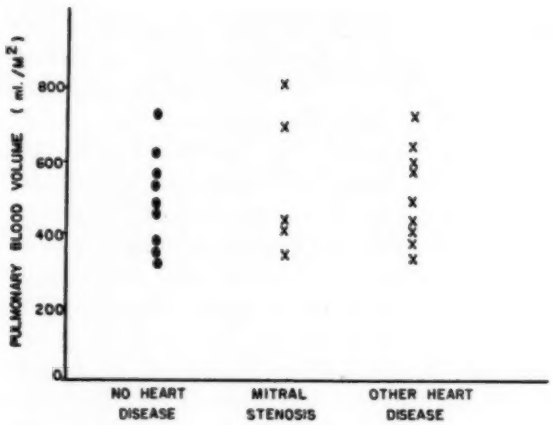

Fig. 6. Division of intracardiac blood volume between the right and left sides of the heart in subjects with normal hearts and in those with ventricular enlargement.

dilution approach. This may be one of the factors responsible for the large variation in results which has been found in this and other studies.[28] No correction for the low hematocrit of small pulmonary vessels has been applied, since this is probably a small error.[29-31]

Many variations of the dye-dilution approach have been applied to the estimation of pulmonary or "central" blood volume. A number of groups have made simultaneous determinations of cardiac output and the time required for substance injected into a vein or the right heart to reach a peripheral arterial site, usually the brachial or femoral artery. An early study employing the fastest rather than the mean circulation time was made by Stewart.[32] Ebert and his associates[33] found that the volume measured by injection into the pulmonary artery and sampling from a femoral artery averaged 605 ml./M.² of body surface, and Doyle and co-workers[34] obtained an average result of 634 ml./M.² when arterial samples were collected from a radial artery. Hetzel and others[35] obtained a mean result of 1,081 ml./M.² with sampling from the radial artery for a similar procedure. Kopelman and Lee[36] reported a mean volume of 1,140 ml./M.² between antecubital vein and brachial artery, and 770 ml./M.² when the injection was given in the main pulmonary artery. Braun and associates[37] found mean total volumes of from 910 to 1,120 ml. measured from antecubital vein to brachial artery, corresponding to approximately 600 ml./M.². It has recently been demonstrated[38,39] that local hyperemia or vasoconstriction of the extremity from which samples are taken has a marked effect on the arterial concentration curve and on central volume determined by this method. In an early study, Blumgart[40] estimated the true pulmonary blood volume to be of the order of 589 ml. total. Lagerlöf and associates[41] injected dye into the pulmonary artery and made corrections for the blood within the arteries and left side of the heart. Values averaging 595 ml./M.² were obtained. Kraus and associates[42] injected dye into the pulmonary artery, and I^{131} albumin into the left atrium simultaneously, and sampled from the brachial artery. The average pulmonary volume in patients with normal dynamics was 260 ml./M.², which is considerably lower than estimates made by any other technique. A similar study by McGaff and associates[43] resulted in a mean figure of 370 ± 40 ml./M.² in 13 subjects with rheumatic heart disease.

Shipley and co-workers[11] have pointed out the feasibility of calculating from the radiocardiogram the mean circulation time from right heart to left heart. They have reported an average value of 6.5 seconds in normal subjects, but no simultaneous measurements of cardiac output were made. Several methods of estimating pulmonary circulation times have also been described by Gigli and associates.[44] Lammerant and DeVisscher[45] have reported determinations of the mean pulmonary circulation time and the circulating pulmonary blood vol-

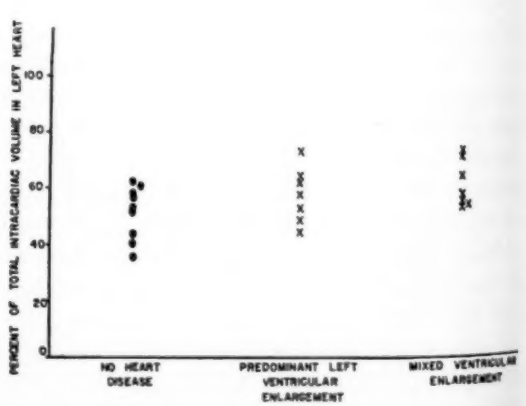

Fig. 7. Pulmonary blood volume in patients without cardiac disease, in those with mitral stenosis, and in those with other types of heart disease.

ume in man by means of I^{131} albumin and precordial monitoring, as has been done in the present study. The mean circulating pulmonary plasma volume in 57 normal subjects was 326 ml./M.², ranging from 195 to 640 ml./M.². This corresponds to a blood volume of approximately 550 ml./M.². These results closely approximate those of the present series. A study by Eich and co-workers,[46] using somewhat different techniques, resulted in a mean estimate of pulmonary blood volume of 436 ml./M.², and another study by Moir and Gott[28] resulted in a figure of 610 ml./M.². The latter authors question the applicability of such techniques to the study of pulmonary blood volume because of the "probable failure of an unpredictable portion of pulmonary blood volume to participate in the primary dilution curve. . . ." The essential agreement of the Stewart-Hamilton technique with the equilibration technique of Bradley as tested by Rabinowitz and Rapaport[47] in dogs is evidence tending to make this possibility less likely, since the time allowed for mixing is increased several fold in the equilibration technique. Attempts at a more direct type of determination based on isotope dilution in blood before and after release of an occlusion of the circulation to one lung have not been convincing.[48] Still another approach is based on the analysis of the slope of indicator curves recorded from a peripheral artery after injection into the right heart.[49] Reasonable figures have been obtained in man,[50] but in comparison with several techniques in dogs[47] the results with this technique were 25 per cent lower than those with the Stewart-Hamilton or Bradley techniques. Hetzel and associates[35] have noted an increase in apparent pulmonary volume when the injection is given at increasing distances proximal to the lung. This finding indicates that the assumptions on which the calculation of pulmonary blood volume by the slope method is based may not apply.

Summary

1. An external isotope method for estimating intracardiac and pulmonary blood volumes has been studied in 41 subjects with and without cardiac disease.

2. Intracardiac blood volume estimated from radioactivity of the cardiac area 10 minutes after intravenous injection of 100 μc of I^{131} albumin averaged 345 ± 55 ml./M.² in 16 subjects without heart disease.

3. In general, intracardiac blood volume was proportional to the size of the heart shadow; but there was slightly less blood in relation to the size of the heart in subjects with cardiac hypertrophy. In 2 persons with pericardial effusion the intracardiac blood volumes were approximately 500 ml. less than would have been expected from the size of the cardiac shadow, suggesting an area of diagnostic usefulness for this technique.

4. By dividing the curve of precordial radioactivity during the first circulation of the isotope into the right and left heart components, the portion of the intracardiac blood in each side of the heart and the pulmonary blood volume were estimated.

5. The right heart volume in subjects without heart disease was 170 ± 25 ml./M.², and the left heart volume was 185 ± 50 ml./M.².

6. In normal subjects, pulmonary blood volume was 490 ± 130 ml./M.². Similar results were obtained in subjects with mitral stenosis and with other forms of heart disease.

7. The isotope methods used in the present studies contain important technical defects. Accurate and reliable techniques will require further development of instrumentation and procedure.

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Case report

Ruptured aortic sinus aneurysm
Case report, with review of clinical features

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With reports during the last 5 years of at least 11 surgical corrections of a ruptured aneurysm of a sinus of Valsalva, the diagnosis is no longer one of academic interest alone.[1-8] It is now a matter of paramount importance that the lesion not only be entertained in the differential diagnosis, but also that the definitive diagnosis be established with minimal delay.

Aneurysms of the congenital variety almost invariably originate from either the right coronary or noncoronary sinus and rupture into the right atrium and/or the right ventricle.[9] The result is an acute aortic sinus–right heart fistula. The characteristic clinical complex usually consists of a young adult without pre-existing evidence of cardiac disease who develops the acute onset of dyspnea and/or chest pain. The typical signs consist of a murmur in both systole and diastole, with maximal intensity about the lower half of the sternum, and evidence of rapid aortic runoff.

However, all of these characteristics are equally typical of a ruptured aortic valve with acute aortic insufficiency, which is the most frequent incorrect diagnosis. When knowledge concerning pre-existing cardiac disease is lacking and the onset is less dramatic, several other lesions might be suggested, particularly patent ductus arteriosus and the various congenital defects which occasionally simulate a patent ductus.

Although the typical murmurs of these lesions are well known, that of an aortic sinus–right heart fistula remains less well defined. Agreement exists that the murmur of the typical defect is present in both systole and diastole; however, there are conflicting reports concerning its exact timing and maximal intensity within the cardiac cycle, as well as the site of maximal intensity upon the thorax. Phonocardiographic registration of the murmur has been infrequently reported: a brief review of the literature revealed only 10 reports in surgically or pathologically proved cases.[1-4,7,8,10-12]

The following case is of interest not only because of the favorable outcome, but from a diagnostic viewpoint as well. Of special interest are the several symptoms and signs which permitted a reasonably confident diagnosis prior to any laboratory studies, and the unusual features of the murmur as confirmed by the phonocardiogram.

Case report

J.L.M., a 31-year-old Negro laborer, was admitted to The City of Memphis Hospitals on Nov. 24, 1959, with a 2-day history of marked exertional dyspnea which was associated with tightness in the upper abdomen. During the previous 6 weeks he had noted a nonproductive cough and a

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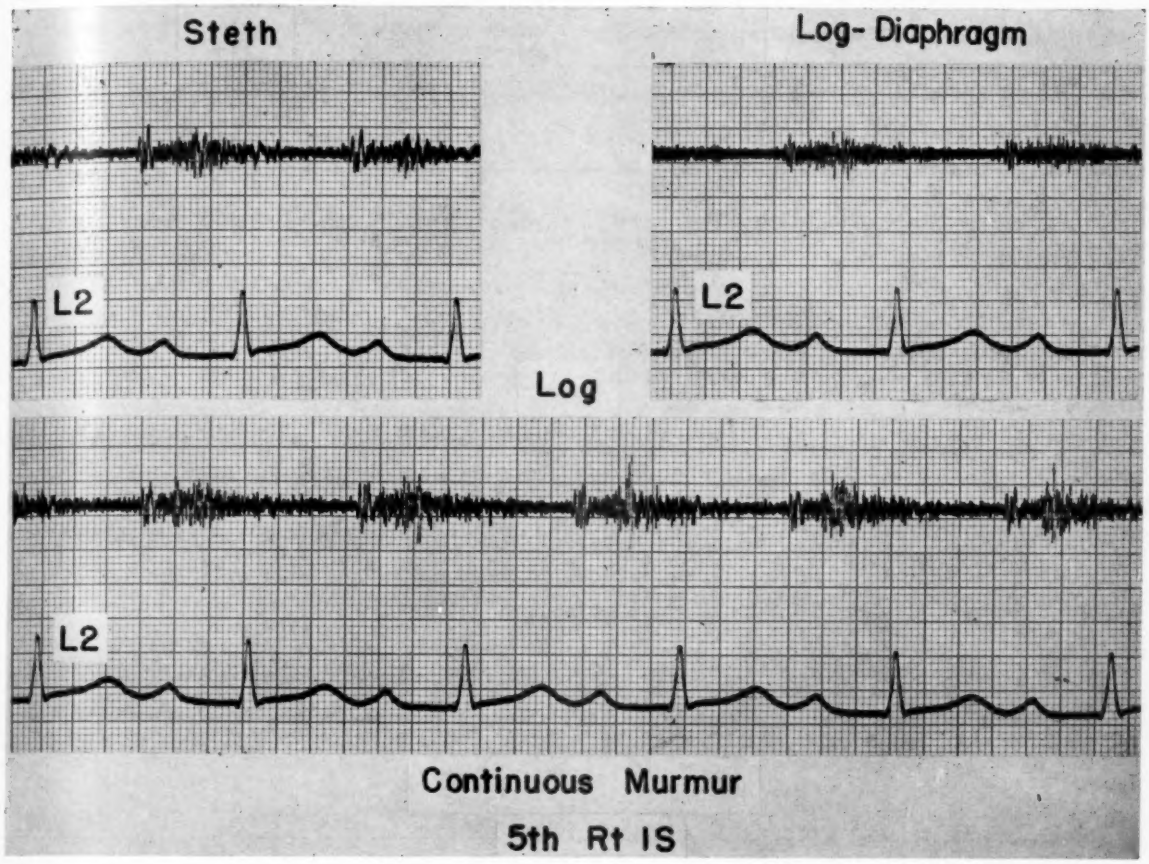

Fig. *1.* Phonocardiogram recorded at the site of maximal intensity of the murmur. Progressively higher frequency components of the murmur are demonstrated in the stethoscopic, logarithmic, and logarithmic with diaphragm tracings, respectively. Note that the murmur is continuous through the first sound, and that the peak amplitude occurs just before mid-diastole.

mild pain in the lower left lateral chest which was not influenced by respiration. His only previous admission was 3 years before, at which time an appendectomy was performed. At that time there was no evidence of cardiac disease by physical or chest x-ray examination.

Although he complained of marked dyspnea, he was nevertheless most comfortable in the supine position. The temperature was 98.6° F., the pulse was regular with a rate of 104, and the respiratory rate was 28. The blood pressure was 140/50-0 mm. Hg, and the peripheral signs of rapid aortic runoff were evident. The neck veins were moderately distended, with a suggestion of a systolic pulsation. A moderately tender liver was palpable 4 cm. below the right costal margin, and a systolic expansile pulsation was detectable. Moist râles were audible throughout both lungs, and there was a trace of pedal edema.

Cardiac examination revealed the apical impulse to be in the fifth intercostal space in the mid-clavicular line, and its character was neither more diffuse nor forceful than usual. Instead, both a slight systolic lift and a diastolic pulsation were visible and palpable in the left parasternal region. An intense thrill, limited to diastole, was palpable in the fourth and fifth right intercostal spaces parasternally. The first sound was diminished, and a moderately accentuated single second sound was heard best in the second and third left intercostal spaces. A marked summation gallop was audible over the mid-precordium. A continuous murmur was best heard in the region of the thrill. The diastolic component was Grade 6 in intensity and harsh in quality; it was crescendo after the second sound and reached a peak in mid-diastole almost synchronously with the summation gallop; after this peak the murmur became decrescendo through the first sound and systole. This systolic component was Grade 2-3 in intensity, with a blowing quality. Both components were also heard less distinctly over the entire precordium. However, the diastolic component was also loudly transmitted to the right and inferiorly, and was easily audible in the epigastrium, over the liver, and at the right anterior axillary line (Figs. 1 and 2).

The ECG (Fig. 3) revealed a first-degree A-V block and a mean QRS axis at 90 degrees. Phonocardiography confirmed the auscultatory findings (Figs. 1 and 2). Chest x-ray film and cardiac fluoroscopy demonstrated moderate pulmonary congestion with minimal right pleural effusion, slight enlarge-

Table I. *Right heart catheterization data*

	Blood pressure		*Blood oxygen*	
	Phasic (mm. Hg)	*Mean (mm. Hg)*	*Content (ml./100 ml.)*	*Saturation (per cent)*
Innominate venous junction	15/10	13	5.6	43
High right atrium	15/10	13	5.9	45
Low right atrium	13/11	12	6.8 } 6.6	52
Mid right atrium	13/10	11	7.2	55
Apex right ventricle	43/16 (d)*	33	9.8	75
Mid right ventricle†	52/16 (d)*	33	10.7 } 9.9	82
High right ventricle	56/5 (d)*	31	9.4	72
Pulmonary artery, proximal position	54/16	32	9.6 } 9.5	74
Pulmonary artery	55/7	31	9.4	72
Left brachial artery	110/46 (d)*	—	11.8	91
Oxyhemoglobin capacity			13.0	100

Systemic blood flow: 6.5 L./min. O_2 consumed: 339 ml./min.
Pulmonary blood flow: 14.8 L./min. Hematocrit: 31 vol. per cent
Cardiac index: 3.6 L./min./M.²

*d: Damped.

†Undamped phasic right ventricular pressure = 55/1-12 mm. Hg.

The low systemic arterial oxygen saturation, wide A-V oxygen difference, and increased systemic blood flow are consistent with high-output left ventricular heart failure. The high systemic venous pressure and elevated end-diastolic right ventricular pressure are consistent with right ventricular failure. A moderate sized left-to-right shunt into the right ventricle is also demonstrated. (The catheterization data were made available through the courtesy of James W. Culbertson, M.D., and Sherman H. Hoover, M.D., Department of Internal Medicine, University of Tennessee Medical Center.)

ment of the right atrium and right ventricle, and equivocal evidence of increased pulsations of these chambers and the pulmonary artery (Fig. 4). The venous pressure was 240 mm. of saline, and the arm-to-tongue circulation time was 45 seconds. VDRL was negative.

Hospital course. The working diagnosis was an acute aortic sinus–right heart fistula presumably secondary to a ruptured congenital aortic sinus aneurysm. Medical management was attempted with digitalization, oxygen, and diuretics, but this treatment resulted in only temporary improvement. He soon resumed a course characterized by extreme dyspnea on the slightest exertion, which was relieved only by his remaining at complete rest in the supine position. Several episodes of acute dyspnea, not precipitated by effort, occurred, lasted 30 to 60 minutes, and then subsided spontaneously.

On the second hospital day the patient became febrile, and bacterial endocarditis was considered. The cause, however, was soon found to be a perirectal abscess, which responded promptly to antibiotics and surgical drainage.

On the seventh hospital day a right heart catheterization was performed (Table I). A major rise in oxygen saturation was detected in the right ventricle and was interpreted as indicative of a left-to-right shunt with a right ventricular exit. In addition, the right ventricular systolic pressure was elevated to 55 mm. Hg.

Because of his relentless course, an open-heart operation during total cardiac bypass was performed on the fourteenth hospital day. A continuous thrill was palpable over the inflow tract of the right ventricle. A fusiform aneurysmal sac was found to originate from the right coronary sinus and overlap the septal leaflet of the tricuspid valve, protruding chiefly into the right ventricle but with a slight bulge into the right atrium. The tip of the ventricular portion was ruptured, resulting in a fistula which opened into the inflow tract. Excision and closure of this ventricular portion produced a rent in the atrial bulge, which required an additional atrial incision for closure.*

Right bundle branch block developed during operation and has persisted since. After the operation, improvement was prompt and otherwise complete. The patient was discharged with neither

*Operation was performed by James W. Pate, M.D., Chief, Department of Thoracic Surgery, University of Tennessee Medical Center.

symptoms nor signs, on no medications, and fully ambulatory. No murmurs have since been detectable by auscultation or phonocardiogram. Six months later the patient remained asymptomatic and had returned to work.

Discussion

Differential diagnosis of present case. Previous evidence of a normal heart and the mode of onset of symptoms were of great value in this case, both strongly suggesting that the defect was acutely acquired rather than congenital in etiology. In addition, the presence of a murmur both in systole and diastole associated with signs of rapid aortic runoff further limited the possible considerations, and suggested that the defect in all probability originated within the aorta.

Regardless of the more specific etiology (i.e., congenital aortic sinus aneurysm, syphilis, dissecting aneurysm, bacterial endocarditis) the diagnosis of the hemodynamic defect per se essentially resolved to a distinction between acute aortic insufficiency and an acute aortic sinus–right heart fistula. Despite other helpful features, the following two findings were of primary importance in this differential, with both as strongly favoring one diagnosis as they opposed the other. (1) *Absence of significant left ventricular enlargement and failure:* In the presence of marked exertional dyspnea and both cervical vein and hepatic engorgement, several findings directed attention to the right rather than the left ventricle: the absence of orthopnea and actual preference for the supine position; the normal location and character of the apical impulse

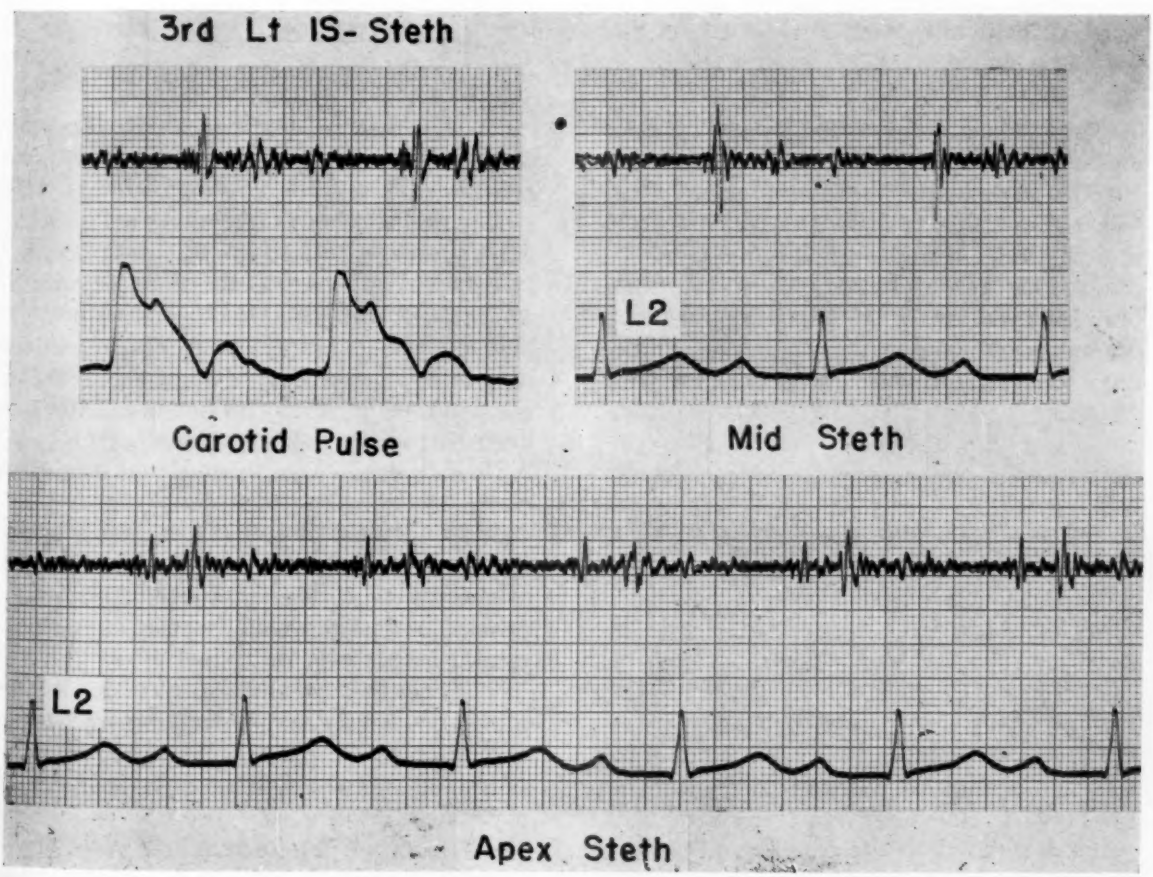

Fig. 2. Phonocardiograms demonstrating the carotid pulse, accentuated second sound, and the summation gallop. Although the higher frequency components of the murmur can be seen in each tracing, they are of much lower amplitude than those recorded to the right of the sternum (Fig. 1). The second sound is best recorded at the mid-precordium and occurs simultaneously with the brief T-P segment. The summation gallop occurs 0.08 second after the summit of the P wave, and although easily evident on all three tracings, it is most prominent at the apex. The gallop varies slightly in amplitude and number of distinct components, apparently reflecting variations in the degree of summation.

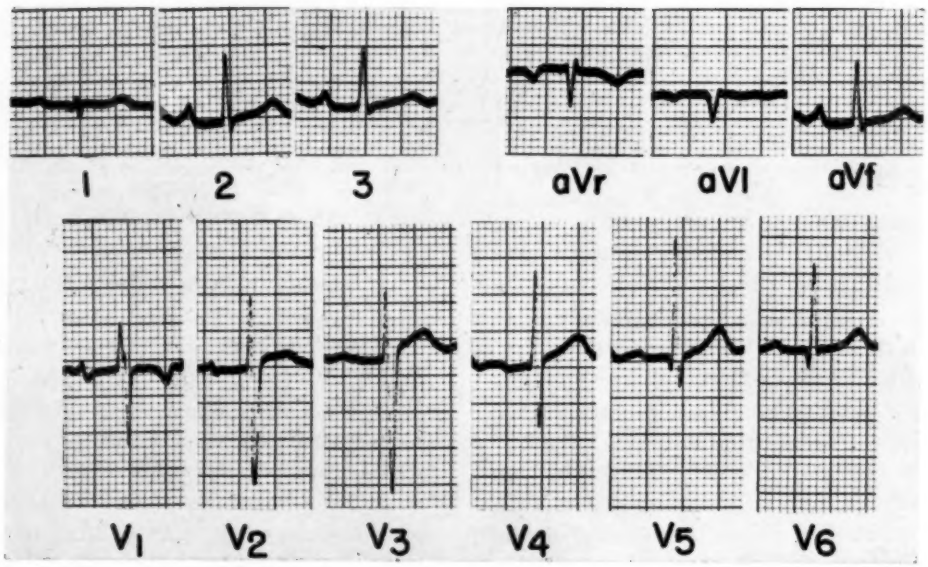

Fig. 3. Electrocardiogram which reveals first-degree A-V block (P-R interval of 0.24 second in Lead II), and the mean frontal QRS axis to be at 90 degrees. In addition, a late peak is evident on the P waves in Leads II, III, and aV_F, and there is a notch on the downstroke of the R wave in Lead V_1.

in contradistinction to the palpatory findings in the mid-precordium which suggested a right ventricular systolic lift and diastolic gallop; a mean QRS axis at 90 degrees in a 31-year-old person, sthenic individual; roentgenographic evidence of right chamber enlargement with possible pulsatory phenomenon, suggesting that the pulmonary congestion was active rather than passive. (2) *Presence of a continuous murmur:* The continuous character of the murmur was the one feature that was of major importance in this particular differential.

The accentuated pulmonic second sound, first-degree A-V block, and the systolic pulsation of the liver and cervical veins were of additional value, although less specific.

Murmur of aortic sinus–right heart fistula. It is probably only rarely that this murmur occurs as an isolated finding. Not only are additional anatomic lesions frequently associated, but a variety of "relative" murmurs, unrelated to the actual shunt across the defect, are often present. In addition, reported cases of aneurysms of the sinus of Valsalva appear to include a broad spectrum of pathologic entities, and encompass almost all diseases known to affect the aortic root and/or aortic valve. For this reason, we have attempted to review these heterogeneous reports, and offer the following description of the murmur as a composite.

The one constant feature of this murmur is its presence in both systole and diastole.[9] It is usually continuous, but not infrequently is composed of separate systolic and diastolic components, and resembles a to-and-fro murmur. It is of moderate to great intensity, with the maximal intensity occurring either in both phases or in systole. A thrill is usually associated, and its timing corresponds to the maximal intensity. Although only rarely are the maximal intensity and thrill limited to diastole,[13] peculiarities in both the character and transmission of the diastolic component in particular have been described.[1,10,14]

The quality of the murmur is usually harsh or coarse, and a "machinery" character is often imparted when it is continuous. It is repeatedly described as having a superficial quality.

The thoracic site of maximal intensity is usually described as "low," and this term is applied in reference to the usual location of a patent ductus murmur. This site is usually between the third rib and the xiphoid, and is variously located over or adjacent to either side of the sternum. Transmission of the murmur is generally diffuse. On occa-

sion, differential transmission of the systolic and diastolic components has been noted, with the diastolic component usually directed inferiorly and the systolic component more frequently directed toward the apex.

The characteristics of the murmur have not been of value in determining the specific origin of the fistula within the aortic root. However, the site of maximal intensity of the murmur and the transmission of the diastolic component may provide clues to the location of the exit.[10] When the exit is within the outflow tract of the right ventricle (as reported in cases of syphilis, bacterial endocarditis, and penetrating trauma), the maximal intensity is often higher upon the thorax (second to third intercostal space); when the exit is within the inflow tract of the right ventricle (usually associated with internal aneurysmal sac as in congenital cases) or right atrium, the maximal intensity is usually located lower upon the thorax (third intercostal space–xiphoid). An unusual transmission of the diastolic component to the right and inferiorly has been suggested to be of diagnostic value of a right atrial exit.[10]

The murmur in the present case was continuous with the site of maximal intensity in the fourth and fifth right intercostal spaces parasternally. In this regard it is consistent with that in previous cases in which the fistula enters the inflow tract of the right ventricle through an aneurysmal sac.

However, the transmission of the diastolic component to the right and inferiorly was identical to that previously attributed to a right atrial exit. It would appear, therefore, that this feature is not quite so specific, and that either a right atrial or right ventricular inflow tract exit may result in this unusual transmission.

Of greater interest, however, is the striking maximal intensity during the diastolic phase. The murmur became crescendo after the second sound and reached a peak in mid-diastole, almost synchronously with a summation gallop. After this it became decrescendo, passing through the first sound and systole. This is contrary to the description in the majority of reports, and one must speculate that perhaps this diastolic accentuation might be of greater diagnostic value than has previously been recognized.

A general anatomic similarity exists between a coronary artery, a coronary A-V fistula, and the congenital type of the present defect; in essence, they all represent fistulous tracts which originate in the aortic sinuses and usually enter the right heart. These similarities raise the question of whether the flow of blood in the latter two defects might be somewhat analogous to that in the coronary arteries—being maximal during diastole.

It is of interest that this analogy to coronary blood flow has been applied in cases of coronary A-V fistula, in which the continuous murmur is not infrequently reported to be maximal during diastole.[8,15,16] However, whereas both a coronary A-V fistula and coronary artery must traverse the myocardium, the present type of defect consists of an internal aneurysmal sac. Thus, the factor of myocardial relaxation, which plays an important role in augmenting coronary blood flow during diastole, is not present. Nevertheless, if the exit of the aneurysmal sac is within the right ventricle, a somewhat similar mechanism could conceivably be a factor as a result of the decrease in intraventricular pressure during diastole.

The origin of these three types of "fistulae" from the aortic sinuses suggests an

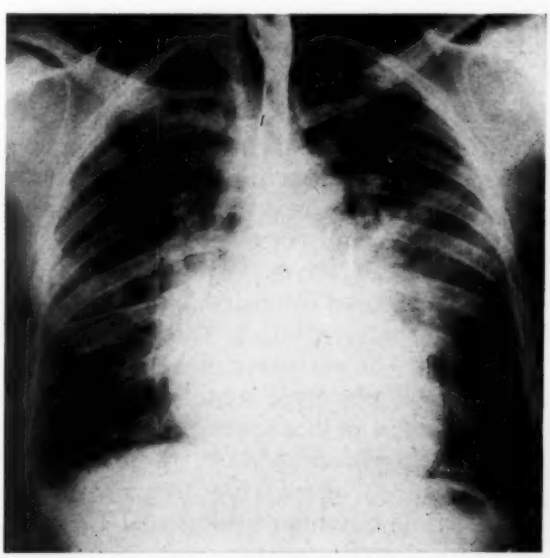

Fig. 4. Roentgenogram of chest taken approximately 4 days after rupture of the aortic sinus, demonstrating globular enlargement of the heart and acute pulmonary congestion.

additional factor in support of such an analogy. Since a Venturi effect may play a role during aortic ejection,[17] it is possible that the pressure within the aortic sinuses is disproportionately decreased during systole. Since quantitative information about this contribution is not available, one can only state what the hemodynamic situation would be if this contribution were sufficient to ensure a maximal aortic sinus pressure during diastole. Under these circumstances, the maximal flow of a left-to-right shunt through any of the "fistulae" would be maximal during diastole; this would be independent of whether the recipient chamber were the right atrium or right ventricle.

These reflections permit some conclusions concerning the circumstances—in at least congenital types of the present defect—in which a diastolic accentuation of the continuous murmur might occur. The combination of an aortic sinus origin and right ventricular exit represent the ideal anatomic situation, and the likelihood of such an occurrence would increase with the right intraventricular pulse pressure. Should the Venturi effect actually prove to be of major importance, a diastolic accentuation might also occur with a right atrial exit; however, this conclusion must rest upon demonstration of it in future cases.

These considerations are of importance in the differential diagnosis of systolic-diastolic murmurs which originate either directly or indirectly from the aorta. Such a murmur produced by aortic valvular disease is, of course, composed of separate systolic and diastolic components. The murmurs of patent ductus arteriosus, aortic-pulmonic septal defect, aortic sinus–right heart fistula, and coronary A-V fistula, on the other hand, are usually continuous. The peak of maximal intensity appears to be of value in differentiating these continuous murmurs. The murmurs of a patent ductus or an aortic-pulmonic septal defect are usually maximal in late systole or at about the time of the second sound[8]; the murmur of coronary A-V fistula has frequently been reported as maximal in diastole. The present report indicates that a similar diastolic accentuation may be present in cases of aortic sinus–right heart fistula—particularly if the fistula consists of an internal aneurysmal sac within the right ventricle.

Summary and conclusions

1. A case of ruptured aortic sinus aneurysm which was clinically diagnosed and surgically corrected is presented. The aneurysm was apparently congenital. Rupture produced an acute fistula between the right coronary sinus and right ventricular inflow tract.

2. The clinical aspects of the case are emphasized, particularly the several features which proved to be of considerable diagnostic value.

3. The murmur presented several unusual features which were documented by a direct-writing phonocardiogram. The characteristic murmur of aortic sinus–right heart fistula as ascertained from the pertinent literature is described. The murmur of the present case suggests two additional diagnostic points: (a) Unusual transmission of the diastolic component to the right and inferiorly may be produced when the exit of the fistula is within the right ventricular inflow tract as well as within the right atrium. (b) A diastolic accentuation of the continuous murmur, when present, may suggest that the origin of the fistula is within an aortic sinus and that the exit is within the right ventricle. An analogy to coronary blood flow and the murmur of coronary A-V fistula is noted.

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Clinical pathologic conference

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Clinical abstract

DR. SOMERS:

First admission.

HISTORY. A 22-year-old Ganda male on his first admission to hospital gave a history of cough and fever which had lasted 3 months. The cough was productive only of scanty white sputum. He denied hemoptysis but thought he had lost some weight. There was no contact history of tuberculosis.

PHYSICAL EXAMINATION. He was a normally developed and reasonably well-nourished patient without evidence of recent loss of weight. Physical signs were confined to the chest. The percussion note was impaired, and there were râles and diminished breath sounds over the left lower lobe. Clinically, the apex beat was in the fifth left intercostal space, within the mid-clavicular line. The heart sounds were normal. There were no murmurs. Blood pressure was 130/90 mm. Hg. The liver and spleen were not palpable; no lymphadenopathy was evident. He did not appear to be anemic. He weighed 105 pounds.

LABORATORY EXAMINATION. Relevant investigations were as follows: hemoblogin, 85 per cent (13.3 Gm./100 ml.); white blood cell count, 12,000/c.mm.; neutrophils, 82 per cent; lymphocytes, 14 per cent; monocytes, 4 per cent; erythrocyte sedimentation rate (Wintrobe), 39 mm./hour. The sputum was purulent, and on direct examination and culture was shown to contain pneumococci. Four examinations for acid-fast organisms were negative.

X-RAY EXAMINATION. There was a shadow of uniform density at the left lung base. The left diaphragm was raised, and the left lateral view showed that the opacity involved the lingula pulmonis. There was thickening of the transverse fissure in the right lung. The heart size and shape appeared to be normal (Figs. 1*A* and *B*)

HOSPITAL COURSE. A resolving pneumococcal lobar pneumonia was diagnosed, and he was started on a course of penicillin.

The fever, which was 103°F. on admission, subsided over the next few days but recurred on the sixth day. It was felt that the organism was probably penicillin-resistant, and tetracycline was given. By the end of the second week the fever had subsided. The patient was discharged with a diagnosis of postpneumonic segmental collapse and was asked to report for breathing exercises and follow-up as an outpatient.

When next seen 2 weeks later, he still had a slight cough. Impaired percussion note and diminished breath sounds were evident at the left lung base. Examinations of sputum for acid-fast organisms were repeatedly negative. Deep-breathing exercises were continued, and a further course of tetracycline was prescribed. A repeat x-ray examination of the chest showed a moderate increase in the heart shadow (Figs. 2*A* and *B*). Although requested to do so, he failed to report again until 2 months later, when again the symptoms and signs in the chest were essentially unchanged. A new sign, however, was the presence of an enlarged left supraclavicular lymph node. Immediate hospitalization was urged but was refused by the patient. His wife was imminently expectant and he wished to make arrangements for her delivery. Several weeks later he was readmitted as an emergency case in an extremely ill condition.

Second admission. On this admission, 6 months after the first, there was an interval history of cough, productive of a scanty amount of white sputum. During the 4 weeks previous to admission he had lost weight rapidly. The cough had become much worse and he was breathless and weak. The sputum had remained nonpurulent, and he denied hemoptysis.

PHYSICAL EXAMINATION. He was an ill, wasted patient, febrile, and with moderately severe dyspnea. The temperature was 102°F., and respirations were 35 per minute. Enlarged, firm lymph nodes were palpable in both supraclavicular regions, left axilla, and both inguinal regions.

The precordium bulged anteriorly. Cardiac dullness was continuous with dullness at the left lung base. On the right side, cardiac dullness was noted up to the right mid-clavicular line. The heart rate was 140 per minute and regular. Blood pressure

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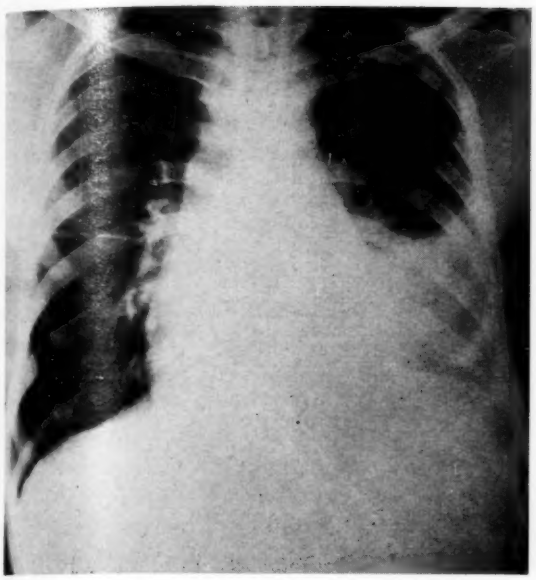

Fig. *1A*. Posteroanterior roentgenogram of chest taken at first admission.

was 110/80 mm. Hg, and a doubtful pulsus paradoxus of 10 mm. was recorded. First and second heart sounds were audible, but they were faint and distant. No murmurs were audible. The mean jugular venous pressure was raised 3 cm. above the sternal angle, and pulsations were evident. At the left lung base the percussion note was dull and the breath sounds were diminished. The liver was firm and palpable, enlarged 4 fingerbreadths. The spleen was not palpable. There was no ascites or peripheral edema.

ELECTROCARDIOGRAPHIC EXAMINATION. The tracing showed a regular sinus rhythm, with a rate of 125. The P wave and P-R interval were within normal limits. QRS complexes showed a low voltage throughout. T-wave inversion was present in Leads V_2, V_3, and V_5. Otherwise, T was flat throughout (Fig. 3).

HOSPITAL COURSE. Pericarditis with effusion was suspected; an immediate pericardicentesis was attempted, but no fluid was obtainable. The patient's condition improved slightly by the next morning, but he became very distressed, restless, and dyspneic 18 hours after admission. The venous pressure had increased. A repeat pericardicentesis again yielded a dry tap. His condition deteriorated rapidly, and he died a few hours later.

Discussion

PROFESSOR WILLIAMS: This was a young man with a history of cough and febrile illness and a moderate neutrophilic leukocytosis. Since he had a history of illness for 3 months, I am surprised that the diagnosis of pneumococcal lobar pneumonia was a confident one, because it is rather a long course for this type of pneumonia. Clearly in the minds of his physicians there was always the thought of tuberculosis, which indeed must have been the thought which came to all our minds in regard to a young man of 22 years with that sort of history: slight loss of weight and productive cough. Thorough efforts seem to have been made to establish bacteriologic evidence of tuberculosis but results were negative. I wonder whether a Mantoux test was made?

DR. SOMERS: I regret that it was not made, Professor Williams.

PROFESSOR WILLIAMS: He was discharged much improved, but there is the point that the pyrexia had dragged on into the second week in spite of antibiotic treatment. When we look at the x-ray films, the factor of pulmonary collapse is evident: the left diaphragm is very considerably raised, although the mediastinum is not displaced. So, at the time of the first admission, there is this history of a rather long illness with considerable pulmonary collapse, and little radiographic change 2 months later when he came back with enlarged lymph nodes. This again raises the question of tuberculosis. The patient did not allow any further investigation at that time, or one would have been interested in the finding on lymph-node biopsy. When he came back the third time, he was really very ill. At

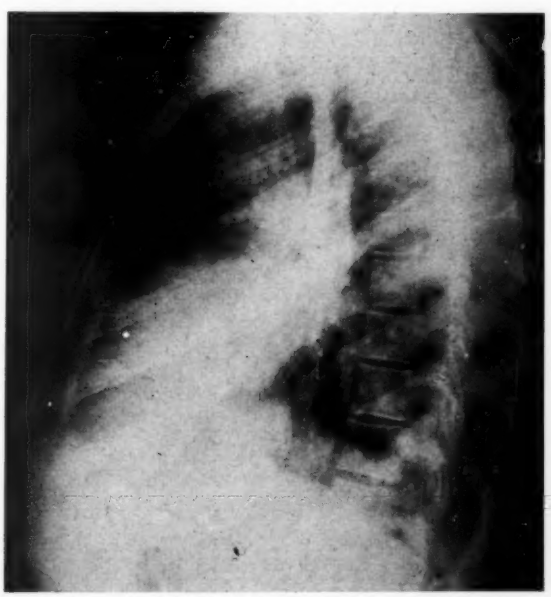

Fig. *1B*. Lateral roentgenogram of chest taken at first admission, showing shadow of collapse of left lower lobe.

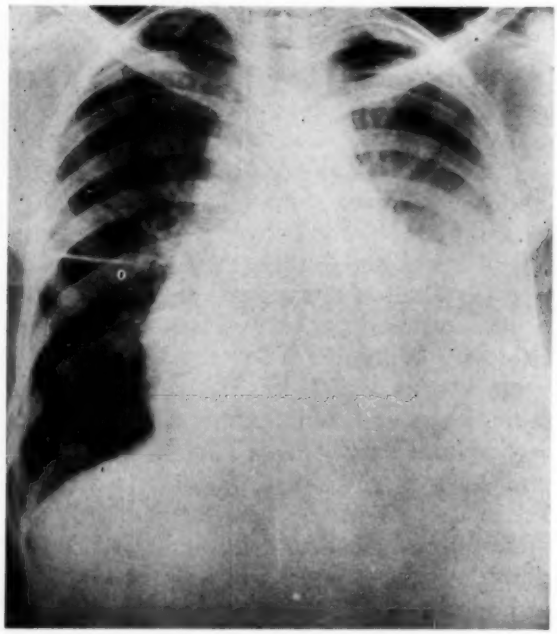

Fig. *2A*. Posteroanterior roentgenogram of chest taken 3 months after admission.

this stage, I think I would have become rather skeptical about a diagnosis of pulmonary tuberculosis, because with this length of duration of the illness and persistent sputum, one would by now have expected the tuberculosis to be positive. But we have no evidence that acid-fast bacilli were ever found. He now had much more extensive lymphadenopathy than before, and he had lost more weight. If one withdraws the diagnosis of tuberculosis, one must surely consider malignant disease. There were now lymph nodes in both supraclavicular regions, left axilla, and both inguinal regions. He had a bulging precordium and increased cardiac dullness. He was too ill at this time for further radiography. The clinical picture brings out a new development, namely, pericardial involvement, with a suspicion of paradoxical pulses, and nonspecific low-voltage cardiogram with T-wave inversion consistent with chronic pericarditis. Again, there was no biopsy at this stage. If it were not for the pericardial presentation, one would be thinking of Hodgkin's disease, with mediastinal involvement of several months' duration and late extension to the peripheral lymph nodes. The spleen was not palpable. One reaches a provisional diagnosis of malignant lymphoma. Carcinoma of the lung is a possibility, except for its unlikelihood in a patient of this age and its rarity in African patients. There was no pericardial effusion, and one wonders why there was so much evidence of pericardial involvement—the huge cardiac shadow, the characteristic raised venous pressure, the cardiographic signs, and paradoxical pulse. He could have had a thickened pericardium, such as one sometimes sees at a certain stage of tuberculous pericarditis. Apart from the lymphadenopathy, if he had had a pericardial effusion at some stage, one would now have been thinking along the lines of tuberculous pericarditis, going on to constrictive pericarditis. Instead of this, however, he started off with a normal-sized heart shadow, with little or no evidence of effusion, and when the heart shadow became large, no fluid was found in the pericardial cavity. It could possibly be a very thickened pericardium, which in the case of tuberculosis can be an inch thick with caseous tuberculous granulation tissues, having much the same effect on cardiac action as an effusion under tension. But usually there would have been an effusion preceding that, and here we have

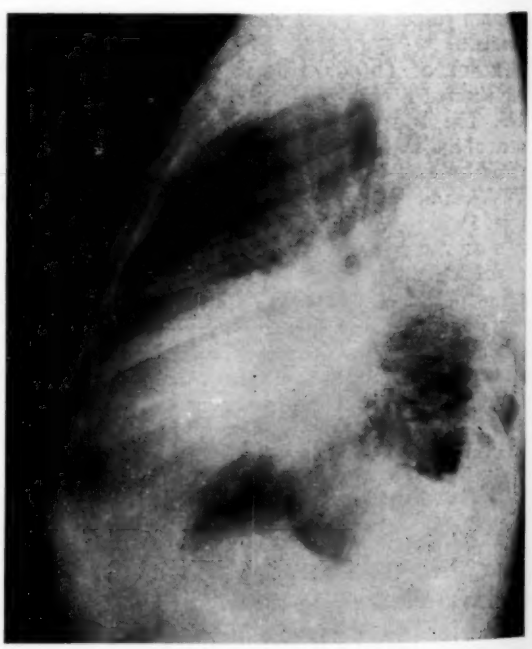

Fig. *2B*. Lateral roentgenogram of chest taken 3 months after admission, showing generalized enlargement of the heart shadow. Left lower collapse remains unaltered.

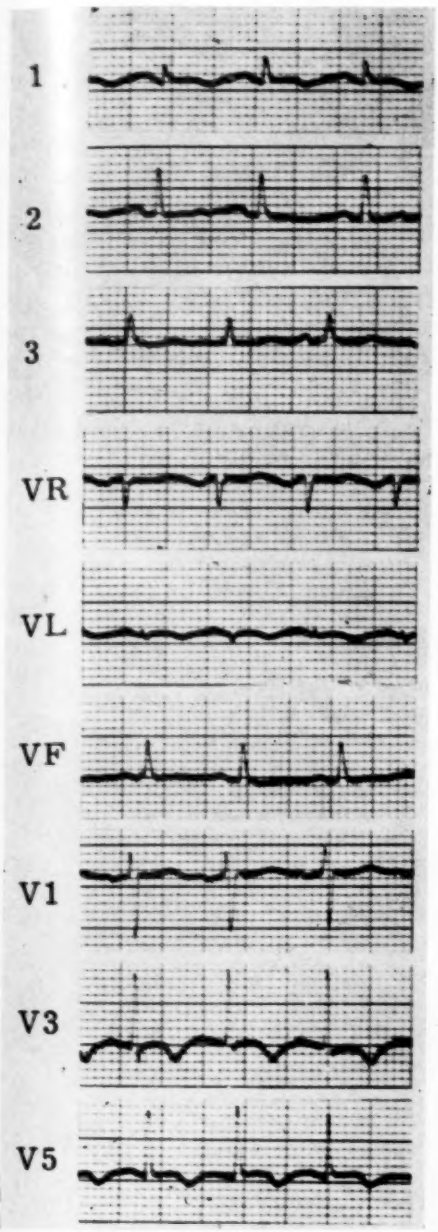

Fig. 3. Electrocardiogram taken on last and terminal admission, showing low voltage of QRS complexes and "T" inversion.

no such evidence. With the extreme wasting and generalized lymphadenopathy, one is left with no alternative for a retrospective clinical diagnosis than that of malignant disease of the mediastinum, probably malignant lymphoma, encroaching on the pericardium. There may possibly have been some dilatation of the heart, but there seems also to have been a great thickening of the pericardium, and it is a question of what type of malignant growth would produce that extensive thickening of the pericardium and at the same time the peripheral lymphadenopathy.

That is as far as I can go. I leave it that this patient died of malignant lymphoma which originated in the mediastinum.

DR. O'CONOR: The anatomic diagnosis was: (1) caseous pulmonary tuberculosis, left lung, with bilateral tuberculous pleuritis—tuberculous empyema, left; (2) productive tuberculous pericarditis with cardiac fixation and tuberculomata of left ventricular myocardium; (3) caseous tuberculous lymphadenitis, generalized; and (4) caseous tuberculosis of thyroid, liver, adrenals.

This patient was found at autopsy to have had a progressive primary type of tuberculosis, with a left-sided empyema and a confluent caseous process involving the entire left lower lobe, lingula pulmonis, and a portion of the left upper lobe. There was an associated obliterative fibrocaseous pericarditis, and multiple tuberculomata were found in the myocardium of the left ventricle. Although there was no pericardial calcification, the heart was completely sur-

Fig. 4. Gross photograph of heart, showing extreme pericardial thickening and myocardial tuberculomata.

rounded by the productive process, which was continuous with a bilateral tuberculous pleuritis. Both ventricles were thus fixed, rigid, and nondistensible (Fig. 4).

In addition to the pulmonary and pericardial disease there was active tuberculous lymphadenitis of all major groups in the neck, chest, and abdomen. Gross and microscopic tubercles and caseous masses were found, as well, in the thyroid, liver, and both adrenals.

Comment

Professor Williams' clinical diagnosis is certainly the major differential one in this case. We are perhaps oversensitive to malignant lymphoma in Kampala, and its high incidence, particularly in children and young adults, keeps the problem ever in mind.

The clinical history and discussion illustrate the difficulty in arriving at a conclusive diagnosis in a specific case, and even at the time of gross dissection it is sometimes difficult to make a distinction between lymphoma and tuberculosis in organs and lymph nodes. It perhaps, therefore, calls for a more liberal use of lymph-node biopsy in the work-up of such a patient, particularly when the sputum is repeatedly negative.

Diagnosis: Tuberculous pericarditis

Annotations

Electrical axis
Measurement and definition in historical perspective

The QRS and T axis is one of the standard items of clinical electrocardiography. However, in about twenty textbooks of electrocardiography, we found in only a few a clear definition of, and clear instructions for, the procedures of determination of the axis. There are some differences in the definition, and the procedure for measurement suggested by some authors is not workable.[1]

One of the most precise definitions and instructions for determination of the mean electrical axis is in the textbook by Burch and Winsor[2]: "It (the mean electrical axis) may be defined as the mean electromotive force (magnitude) of depolarization or repolarization, acting in an average direction during the period of electric activity. It is a vector quantity in that it has magnitude, direction and sense." It is determined from the algebraic sums of positive and negative amplitudes in Leads I and III, plotted on the Lead I and III axes, using the triaxial reference system. In the textbook by Graybiel and White,[3] determination of the "electrical axis" from the net amplitude (algebraic sum) in Leads I and III is recommended, as the "commonly used method" (1946). Ashman and Hull[4] also state that the mean or average electrical axis of the QRS complex is "ordinarily determined" by the algebraic sum of the amplitudes of R and S in Leads I and III, but for the correct determination the net area (algebraic sum of the areas of upward and downward deflections) should be used.

All electrocardiographic textbooks and publications on determination of axis refer to the classic paper by Einthoven, Fahr and De Waart[5] (1913) for the original concept of the electrical axis. However, instead of the term "axis," these authors used the term "direction" of the *instantaneous* vector (Richtung des resultierenden Potentialunterschiedes), but the term "direction" is equivalent to the "axis." They determined the direction of the maximal instantaneous vector in various conditions by taking the R-peak amplitude in two of the three standard leads. They were aware of possible phase differences in the three standard leads. However, they did not suggest determination of the axis from algebraic sums of positive and negative deflections. This was also not done in any of the subsequent publications of Einthoven or his associates, and would not have been compatible with Einthoven's concept (Fahr[6]).

In the same year (1913), Waller[7] published a paper in which he used the term "electrical axis." Probably, this is the first time that the term "axis" was used in the electrocardiographic literature. However, Waller's leads and procedure for the determination of axis were different, and his publication now is only of historical interest.

Carter[8] probably originated the use of the algebraic sum of the amplitudes of positive and negative deflections for measurement of axes. Dieuaide[9] seems to have been the first one to use the term "electrical axis" in a sense which was consistent with Einthoven's original concept.

In 1934, Wilson and his associates[10] introduced the term "*mean* electrical axis," defined as "the axis of the doublet at the center of Einthoven's triangle which develops the mean electromotive force of the heart during the QRS interval. This axis can be determined from the manifest area of the QRS complex of any two of the limb leads." A similar definition was given for the T wave. As a matter of fact, the instructions in current textbooks in regard to measurement of area are fairly precise, in connection with the determination of ventricular gradient.

However, in the clinical application of the concept "mean electrical axis," the measurement of QRS and T areas with a planimeter or by other techniques is time-consuming and, therefore, less practical. As mentioned above, the algebraic sum of R and S in Leads I and III as a substitute (although less accurate) for the determination of axis was suggested by Ashman and Hull.[4] The difference in the determinations of axis from the net area and the net amplitude is relatively small for unidirectional and smooth deflections, since the correlation between amplitudes and areas is high (for QRS: $r = 0.82$; for T : $r = 0.88$).[11] The mean T axis can be determined more reliably from the amplitudes than can the QRS axis.[11] However, in diphasic or bizarre QRS or diphasic T, the difference may be substantially larger, as verified by calculation. Theoretically, the ratio of net amplitude to net area may vary in diphasic deflections quite widely, depending on their configuration. The use of amplitudes multiplied by one half of the duration of the deflection may be practically workable, which is close to Schaefer's suggestion.[13]

The determination of axis from algebraic sums of deflections is now generally accepted, a large amount of data has been accumulated with this technique, and no change is suggested. However, one should be aware of the limitations of this pro-

cedure, and know that this definition of electrical axis and procedure of measurement does not correspond to Einthoven's concept.

The axis in Einthoven's original concept, determined from maximum unidirectional amplitudes, has a different meaning; it is closely related to the axis of the maximum vector of the QRS and T loops in the frontal plane, such as plotted by Burch and associates in their vectorcardiographic research.[12]

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Willem Einthoven
Some historical notes on the occasion of the centenary celebration of his birth

The first Edward K. Dunham Lectures were given at the Harvard Medical School on October 21 and 22, 1924, by Professor Willem Einthoven. The title of his lectures was "The Relation of the Mechanical and Electrical Phenomena of Muscular Contractions, With Special Reference to Cardiac Muscle." During his brief stay in Boston at that time, some episodes of historic interest occurred. I had never met Professor Einthoven before, but inasmuch as the Peter Bent Brigham Hospital was the first hospital in New England to establish an electrocardiographic laboratory, and the hospital was only across the street from the Medical School, he paid us a visit. He and I were seated in the electrocardiographic room chatting about one thing or another, when Miss Bertha Barker, our devoted and efficient technician, brought in a wet electrocardiographic tracing that she had just taken and developed. She interrupted our conversation and asked me whether she should telephone the medical house officer on the wards and tell him that the patient had an acute coronary thrombosis. The understanding in the laboratory was that if a tracing were taken and showed certain changes with which Miss Barker was quite familiar, she was to telephone the intern directly and not wait until the following morning at 9 o'clock, when I usually read all the tracings of the previous day. When I looked at the electrocardiogram she had just taken, I confirmed her diagnosis of acute coronary thrombosis and she left. On overhearing this conversation, Professor Einthoven was amazed. He remarked, "Do I understand correctly that this lady who is not a physician can make a diagnosis of acute coronary thrombosis from the electrocardiogram, without seeing the patient?" Apparently, he had not as yet become familiar with the work done in the United States on the electrocardiographic diagnosis of myocardial infarction. Although the first real publication on the changes in the ventricular complex that occur in acute myocardial infarction appeared in 1920 (Pardee), and was already known to a few of the leading cardiologists in Europe, it had escaped Einthoven's attention. When I showed him some

of these tracings, he was not only amazed but greatly delighted to learn that the instrument which he had devised had such great practical value.

That same afternoon he attended a tea given in his honor, by Dr. Francis W. Peabody, in Cambridge. A goodly number of the members of the faculty of the Harvard Medical School were present at this friendly gathering. Someone there, while chatting with him, remarked in a jocular fashion that he should be getting the Nobel prize for the original, valuable, and fundamental work he had done in the field of electrocardiography. He obviously could not make any real reply to this observation, and the party continued in the customary fashion. I had previously made a dinner engagement with him to dine with me at the Harvard Club in Boston that evening at 6:30.

I arrived at the Club some while before the appointed time, and while waiting, read the evening newspaper. Suddenly, just by chance, I ran across an item about Professor Einthoven. Here was a news dispatch stating that he had been awarded the Nobel prize in medicine. When Einthoven appeared, I immediately congratulated him on this great and well-deserved honor. He was astounded, since he knew nothing about it. In fact, he doubted it. He said that it must be hearsay or gossip which had probably stemmed from the joking that had been going on at the afternoon tea party. He suggested that some newspaper reporter may have been present there or heard of the whisperings and casual remarks that were going on in Cambridge. He added that a colleague of his had been congratulated prematurely, in a previous year, on receiving the Nobel prize, as a result of some news that proved to be unfounded. Suddenly, he asked me whether the newspaper item I had read was a local report or an overseas communication. I had not paid attention to this point, but on quickly looking through the newspaper again I found that it was an overseas report from Stockholm. On seeing this, Professor Einthoven became convinced that it was valid, and naturally was very happy on learning this news. It was not until the next morning that he received the official cable from Stockholm which told him about the great award.

So, one can say that Einthoven's visit to Boston in October, 1924, was memorable in three ways. He gave the first of the celebrated series of the Dunham Lectures. Here he also learned for the first time that the physiologic instrument which he had devised, and with which he had established the early fundamental knowledge concerning the electrical impulses of the heart, was also destined to be of great value in the diagnosis and care of patients with coronary and heart-muscle disease. Finally, it was in Boston that he first learned that he was to receive the celebrated and much honored Nobel prize in medicine.

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Air embolism

The entrance of air into the circulatory system may or may not be fatal, depending among other things on the volume of air injected and the rate of injection. It has been estimated that at the same rate of injection the minimal lethal volume of air entering the right side of the heart is seventy times that entering the left side.[1] Sudden death after the entrance of air into the left side of the heart is due to occlusion of the coronary arteries; death also follows occlusion of the cerebral arteries by the same volume of air, but in dogs this occurs only after many hours.[2] So long as the heart can maintain normal arterial perfusion pressure, air will be pushed through the capillaries into the venous circulation. That air under normal systemic perfusion pressure will readily pass a capillary barrier is not generally appreciated.

In the coronary arteries, air acts as an effective obstruction even though it can readily be propelled through the myocardial capillaries into the coronary veins. The explanation for this seeming paradox is simple. After injection of air into the left side of the heart, air bubbles are plainly visible in the epicardial arteries. With each cardiac systole the proximal part of the intra-arterial air bubble is advanced more than the distal part, because of the relative compressibility of air. This dampens systolic thrust and coronary flow so effectively that myocardial oxygenation is impaired. As the myocardium becomes more anoxic, the vigor of systolic thrust fails and perfusion pressure rapidly drops to zero. Geoghegan and Lam[2] demonstrated that this sequence of events can be reversed if the coronary arterial pressure is maintained at normal levels. They did this by clamping the aorta and applying cardiac massage, maneuvers impressively simple to employ during thoracic or cardiac operation, at which times the hazard of air entering the left side of the heart is well known.

An unexplained phenomenon which regularly follows the embolism of air into any systemic artery is an immediate rise in arterial pressure.[3] The abrupt occurrence of this rise within a few heart beats suggests that it is an autonomic nervous reflex. Teleologically, it seems logical that the body would attempt to force the obstructing air through the capillaries. After this initial event a different reaction occurs, and in the human forearm it has been demonstrated that arterial air embolism is followed by a prolonged period of vasodilatation, the exact mechanism of which is also not understood.[4]

There are some misconceptions in regard to the

effect of venous air embolism, one of which is the belief that air obstructs the pulmonary valve or main pulmonary artery. That this is unlikely is apparent from the demonstration that air, under adequate pressure, will easily pass through the capillaries. Additionally, a routine experiment for students in Wiggers' physiology laboratory has been the demonstration that venous air embolism is immediately followed by hypertension in the pulmonary arteries, due to obstruction of the pulmonary arterioles or capillaries.[5] This is difficult to explain if there is effective obstruction by air at the level of the pulmonary valve.

Although air in the pulmonary capillaries can be pushed through by sustained pressure, just as anywhere else in the body, there are two factors which influence this event in the lungs. First, the normal pressure in the lesser circuit is less than a quarter of systemic pressure. Second, accidents associated with the introduction of air into the veins commonly involve large volumes of air (as in positive-pressure transfusions or hysterosalpingography or presacral injection of air). Such large volumes of air simply fill too extensive a portion of the capillary bed for the relatively low perfusion pressure to dispel it.

If turning the victim of venous air embolism into certain body positions is helpful, as numerous reports of single human cases and some animal experiments suggest, the mechanism of this benefit is not clear. Roentgenographic studies in animals have shown that improvement when the animal is placed in the left lateral decubitus position with head dependent is associated with displacement of an air bolus from the right ventricular outflow tract and pulmonary artery to the right ventricular apex.[6] It does not necessarily follow that the bolus of air was obstructing the flow of blood, particularly in view of experimental evidence that pressure in the pulmonary artery beyond this point is high. It seems more logical to assume that the air bolus is only incidentally located in the right ventricular outflow tract, because of prior extensive obstruction of the smaller pulmonary arteries by air.

Displacement of the air bolus to the apex of the right ventricle by altering body position does two things. First, it replaces between the pump (the right ventricle) and the area of obstruction (the distal pulmonary vascular bed) a relatively incompressible substance, blood, instead of a compressible one, air. Systolic thrust, no longer dampened, is rendered efficient again. Second, the displaced air bolus is churned up with blood and sent into the lungs at a slower rate.

The minimal uniformly lethal volume of air entering the canine *left* heart suddenly is about 1.5 c.c. per kilogram of body weight. Seventy times as much air must enter the right side of the heart for uniformly lethal results. If one could translate data from animal experiments to human subjects, a 60-kilogram human being might conceivably tolerate the sudden entrance of up to 90 c.c. of air into the left side of the heart, and up to 6,300 c.c. into the right side of the heart!

It is quite likely, as numerous investigators have indicated, that the type of gas entering the circulation is important in determining its effect. For example, the high solubility of carbon dioxide in blood makes it relatively less noxious. If any gas enters the coronary arteries, however, where the only opportunity for entering solution is along the relatively small interface between the gas bubble and blood, the factor of solubility becomes less significant. Despite experimental reassurance from animal studies on the entrance of carbon dioxide into the left heart,[7] its use as a contrast substance for intracardiac roentgenography in human beings should be conservatively deliberated if the possibility exists that as much as 90 c.c. may reach the left side of the heart.

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What can be found in arterial pulse waves

Since their earliest registration, the arterial pulse waves have tantalized investigators as a likely, fruitful source of information about the cardiovascular system. Physiologists, with varying degrees of success, have analyzed waves to obtain basic information about the characteristics of the peripheral blood vessels, about peripheral blood flow, and about the dynamics of cardiac function.[1] The clini-

cian has more recently begun to make judgments about the degree and nature of pathologic changes in the peripheral vascular tree on the basis of pulse waves.[2] A brief evaluation of currently available methods for detecting, recording, and analyzing these waves seems in order.

Ideally, the arterial pressure pulse should be measured by direct connection of an appropriate pressure transducer to a needle or catheter in the lumen of the vessels. Such a system should, when properly chosen, yield an absolute, faithful display of the changes in pressure as a function of time.[3] A vast amount of information has been obtained by this approach, but, unfortunately, the trauma involved in direct intra-arterial puncture makes it unacceptable for routine clinical diagnostic purposes. Therefore, alternative methods applicable to large groups of individuals have been developed. These indirect techniques generally measure changes in volume or deformations of a single artery, e.g., with a sphygmograph, or a circumscribed tissue, by means of an oscillometer or plethysmograph.[4] Such indirectly obtained curves are not fully acceptable as a substitute for intra-arterial pressure records, since there is always the tacit assumption that change in volume of the part is a direct, linear function of the change in pressure in some artery. It is unlikely that this assumption is ever entirely valid, and probably fails completely under conditions of sclerosis and other modifications of arterial distensibility.[5] Nevertheless, empirically, such measures of the state of the peripheral circulatory tree have proved to be of great practical value. Curves of this type can be subjected to various analytical techniques to give data that are often of value in clinical problems.

Simple, direct, visual inspection of the curves will often permit differentiation between the normal and abnormal. A normal curve obtained with a digital plethysmograph is characterized by a rapidly rising anacrotic limb, a well-defined dicrotic notch, and a relatively short crest time; in contrast, in the presence of an arterial obstruction, the curve is characterized by a low amplitude, a slowly rising anacrotic limb, rounding of the apex, diminution or absence of a dicrotic notch, and a delayed crest time. More sophisticated analyses and comparisons of pulses have been made with mathematical or instrumental adjuncts. In our laboratory, four different approaches have been used to analyze a single curve.

1. Differentiating circuits give a direct trace of the *rate of change* of the volume of the part at any time during the pulsations.[6] The derivative curve is highly sensitive and tends to amplify small changes in the primary curve, which may not of themselves reveal any visible differences. This technique has detected the presence of disease in individual digits of an extremity, as well as cases of unusual sensitivity to nicotine, epinephrine, or cold.

2. More exact analysis of an individual pulse curve can be obtained by use of the mathematical technique of Fourier analysis. The complex mathematical operations make it desirable to use proper computers for such analysis. The method determines the characteristic group of sine waves which would be required to build the complex curve obtained from the pulsation. Consideration of the specific frequency, amplitude, and phase relationships of these sine waves would provide the basis for a very powerful method. Thus far it has become apparent that arterial obstructive vascular disease results in large changes in the amplitude of high-frequency harmonics, with large alterations of phase angles. The Fourier analysis may be made more revealing by determining the transfer function which compares the harmonic elements from waves taken at two parts of the body, for example, above and below an obstruction. In this way, fine changes in pulse waves produced by vascular abnormalities may be detected.

3. Two pulses may be compared by the simple subtraction of one from another.[7] This can be achieved electrically by subtracting a signal proportional to the volume of one part from that of another. If the two parts are changing in an exactly parallel fashion, the difference curve remains a straight line; if there are even minor differences between the two curves, a characteristic pattern is drawn.

4. Vectorplethysmography makes use of a cathode-ray oscillograph to compare two simultaneously obtained curves. One curve is placed on the X axis of the scope and the other on the Y axis of the scope, and if the two curves are exactly symmetrical and equal, the result is a trace at 45 degrees with the horizontal. Any deviation from identity modifies the line drawn on the scope. With beginning disease the only change in the curve is a modification of amplitude, which results in a change in the angle of the vectorplethysmogram on the scope. With moderate disease the pulses recorded from a normal and abnormal extremity differ sufficiently so that the resultant vectorplethysmogram has the form of an open loop rather than a straight line. In advanced disease, when there is some delay in the transmission of the pulse on one side, the open loop takes on a characteristic form in which there is initially a vertical rise or a horizontal deflection before the curve assumes an angular movement. This vertical or horizontal travel is a measure of pulse delay. In addition, the vectorplethysmogram has proved useful in detecting multiple lesions in a single extremity and in localizing, with some precision, the exact point of obstruction in an artery.[8]

Although important clinical information can be obtained from externally recorded volume curves, additional conclusions can be drawn if one considers the local intra-arterial pressures as well. For clinical purposes the auscultatory method or the plethysmographic method of estimating the pressure is satisfactory. For example, with obstructive arterial disease, low rounded pulse curves with delayed crest times and a lack of dicrotic notches are characteristically associated with low systolic and diastolic blood pressures. With a stiff vessel wall the volume curves are of low amplitude but of nearly normal form; rate of rise is rapid, the dicrotic notch may be small, and the arterial pulse pressure is wide. A relaxed vessel wall is characterized by volume curves of high amplitude, often with a large dicrotic notch with a normal rate of rise of the anacrotic limb; the arterial pulse pressure is normal or low. With an increase in the cardiac output the externally

recorded volume curves are of high amplitude and nearly normal form, and the arterial pulse pressure is high.

A careful analysis of pulse waves is of particular clinical value in discovering the presence and location of obstruction in the arterial tree.

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Letters to the Editor

Detergent between electrodes and skin

Grand Rapids, Mich.
November 5, 1960

To the Editor:

The standard coupling agent between electrocardiographic electrodes and skin is a paste containing glycerin, tragacanth, and sodium chloride.[1] It is recommended and sold by manufacturers of electrocardiographs and, so far as I have been able to determine, is generally used. A search of the literature of recent years has failed to turn up any suggestions for a different coupler.

The paste is slightly irritating to some skins, is sticky, must be washed off, usually gets on the operator's fingers as he fastens the straps, and must be sponged from any clothing or bedding that it touches. The electrodes and straps must be washed carefully after each use, or a sticky residue remains and may corrode metal.

The ability of a detergent solution to conduct electricity was brought to our attention by chance. Such a solution was left in a small sterilizer in which heat is produced by an electric current passing through water. The current was turned on, and the fuse in the circuit burned out instantly.

So, we substituted a solution of detergent for the traditional salt paste on the skin and electrodes, and obtained tracings identical with those made when we used the paste. A mixture of one part of liquid detergent in 100 parts of water is applied with a dropper to the skin under the raised edge of the electrode in position. The chest electrode is dipped in the solution and placed in position on dry skin. If there is much hair, a "brushless" shaving cream serves well with a suction electrode.

When the electrodes are removed, a single wipe with cleansing tissue is all that is necessary for the skin. Electrodes and straps are also quickly cleaned. The total time for the test is appreciably shortened.

Many other substances could be used as coupling agents. However, the wetting and conducting properties, absence of irritation, cleanliness, and ready availability of detergents go far to recommend them for this purpose.

The illustration shows comparative tracings.

Paul W. Kniskern, M.D.

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P. S. It has just come to my attention that the *American Journal of Cardiology*, October, 1959, published a Letter to the Editor from David Littman, M.D., Veterans Administration Hospital, West Roxbury, Mass., in which he describes the use of solutions of salt, glycerin, propenol, and of salt and alcohol. These were found to serve very well.

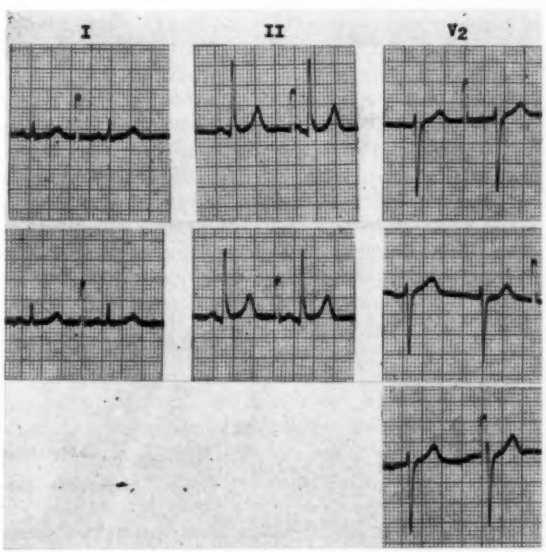

Fig. *1*. Comparative tracings. *Top row:* Detergent on all electrodes. *Center row:* Paste on all electrodes. *Bottom row:* Detergent on limb electrodes, shaving cream on chest electrode.

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November 21, 1960

To the Editor:

The point that care in derivation of the vector loops is required, especially in relation to phase in the lead tracings, is very important and actually underlines an essential precaution in deriving the loops. This in itself makes derivation a technical problem electronically, and even if it is derived perfectly from this aspect cannot yield more in-

formation from the practical standpoint than is contained in the original surface action currents from which it is derived. Furthermore, different frames yield different derivations. The difficulties in relation to the acceptance of a standard frame still remain, especially when one recognizes that Vanremoortere (1956) has shown that decrement of potentials in a homogeneous cylindrical medium is not completely understood. Vector derivation depends on theory which is as yet deficient mathematically for man. As stated by the author, the varied resistances in the body have been recognized for a long time, and have been considered especially by Kaufman and Johnston since 1943. In fact, the conclusion drawn by them is one of the points indicating that the three-dimensional display of Trethewie should be satisfactory in practice.

The fact remains that should vector derivation be possible with complete accuracy, which, even with Schmitt's brilliant researches, is still not possible, no further information can be derived from such vectors than is contained in the original two-dimensional tracings. Furthermore, reading of such vectors is difficult, even though this has improved with projection to three flat planes.

It is desired to stress that vectors cannot demonstrate any further practical information than can be obtained from surface tracings, and this includes the more recent evidence on heart block and infarction. The dipole concept actually was not argued but the electrical source at the heart is exceedingly complicated, even if it is regarded as an almost infinite number of dipoles appearing and reappearing in specialized sequences and directions, as was stressed in a recent publication by Trethewie (1958).

R. Douglas Wright, F.R.A.C.P.
Professor of Physiology

Utrecht, Netherlands
September 29, 1960

To the Editor:

The annotation "Electrocardiography" by Dr. R. Douglas Wright (*American Heart Journal* 60:154, 1960) might give a wrong idea of the recent situation of ECG and VCG.

The opinion that "such a derivation rests on two false premises" (p. 155) could give the impression that this criticism is meant for VCG in general. As to the first point mentioned, the applicability of the dipole conception, valuable work has been done to verify this assumption. Several lead systems of VCG take into account the effect of the position of the dipole. The effect of the varying specific resistance in the trunk was taken into account many years ago. As a second point, the author states that different lead systems give different results. This fact has not been neglected by investigators in the field of vectorcardiography. Opinions vary between the optimistic view that these differences are of minor importance and the more pessimistic view that there is still essential work to be done on this subject. But certainly most investigators agree that there are reasons to choose one of the systems which have a sound physical basis, in order to avoid too great a divergence between lead systems.

The method of Trethewie, recommended by Dr. Wright, has some advantages over the recording of loops and has been recommended and used by some other authors, too. The records of the three components of the heart vector can comprise just the same information as that found in vector loops with time marks. But this is true only if the phase relation between the components can be derived from the records with sufficient accuracy. It is just one of the advantages of VCG to give a result in which these phase differences are displayed in a way that is adapted to the property of the human brain to recognize a shape. The VCG loops give details of shape on such a great time scale that it is difficult to compete with that in ordinary graphs giving the components of the heart-vector as a function of time.

The field of ECG, including VCG, is too vast to be summarized in a single page. It is certainly an extremely difficult task to give a clear review of the main points of the recent developments in this restricted scope. I fear that the author has not succeeded in doing so.

H. C. Burger, Ph.D.

Book reviews

WIEDERHERSTELLUNGSCHIRURGIE AN HERZ UND HERZBEUTEL. By Prof. Dr. Med. W. Schmitt, and Prof. Dr. Med. J. Kudász, Berlin, 1959, VEB Verlag, 232 pages, 143 illustrations. Price: DM 36,80.

This is a book summarizing the present status of surgical therapy of acquired and traumatic heart disease.

The first chapter is by J. Kudász about surgical repair of acquired valvular disease, cardiac aneurysms, and therapy in coronary heart disease. It gives an excellent description of preoperative diagnostic measures. The author's own experience of 1,400 commissurotomies, his critical attitude, and the inclusion of 300 references make this chapter a valuable contribution to the standard literature.

W. Schmitt gives a detailed description of penetrating heart injuries, reports of which he has collected from the literature. The clinical symptomatology is discussed and offers a good review not only to heart surgeons but even more to general surgeons.

Foreign bodies of the heart by W. Schmitt contains also a thorough collection of many cases from the world literature.

Diagnosis and therapy of unexpected intraoperative cardiac arrest by Blume includes an outline for a strict and good therapeutic regimen. The undesired hypotensive side effect of procaine amide (Pronestyl), however, is not mentioned.

Diagnosis and surgical management of pericardial disease, with special reference to cardiac tamponade and constrictive pericarditis, are discussed by Schmitt.

It might be of interest that reference is made to a great deal of Russian literature.

The paper is good, but the printing is sometimes irregular, and the reproductions are not always satisfactory.

ATELECTASIA PULMONAR. By Antonio Jose de Amorim Robalo Cordeiro, Second Assistente da Faculdade de Medicina de Coimbra, Coimbra, 1959, Coimbra Editora Limitada, 518 pages.

The author's work represents the thesis for the M.D. degree which was presented at the Faculdade de Medicina de Coimbra.

The work is divided into two parts. The first one presents the broad problems of pulmonary atelectasis. This section contains three chapters: (1) Fetal and newborn atelectasis: In this chapter the author tries to give a detailed presentation of pulmonary embryology, followed by his concepts concerning the problem of newborn atelectasis. (2) Obstructive bronchopneumopathy: The etiology and physiopathology of the pulmonary ventilatory defects are summarized, and the pathologic aspects, evolution, and differential diagnosis of the various obstructive bronchopneumopathies are discussed. Also described are a great deal of personal experiments performed in laboratory animals. (3) Position of atelectasis in pulmonary pathology: Two main aspects are studied—(a) acquired atelectasis viewed as a return to the fetal state, and (b) the real magnitude of the problem in medicine.

The second part of the work is devoted to circulatory physiopathology of pulmonary atelectasis and is divided into four chapters. (1) The author discusses the physiopathology of the pulmonary arterial circulation and bronchial arterial circulation as well as the bronchial circulation and the bronchopulmonary arterial anastomoses. (2) With regard to the chapter on clinical investigation and hemodynamics, the author contributes 18 cases which have been thoroughly studied. (3) In the chapter pertaining to experimental investigation, the author describes methods for the study of the bronchial circulation and of the bronchopulmonary arterial anastomoses. He reviews a large number of experiments trying to explain the behavior of the bronchial circulation as related to: (a) pathology of the pulmonary arterial system, (b) obstructive bronchopneumonia, and (c) bronchopneumonia in general. He ends the chapter with a pathogenic and physiopathologic synthesis. (4) Final commentary is made on the findings related to the circulatory alteration in the atelectatic lung.

The work ends with a summary in Portuguese (translated into French and English), conclusions, and 909 bibliographic citations.

A reading of Dr. Robalo Cordeiro's book shows clearly that he has done wonderful work. He took up a subject which has been thoroughly debated, informed himself of nearly everything that had been published up to the present date, discussed intelligently the points of view defended by several researchers, and tried to make up for the existing lapses.

We have an excellent impression of the work. The author is extremely careful in his clinical observations, is strict in his experiences, and very cautious in his conclusions. We think that his contribution is extremely valuable. The work would seem to be very useful to those who wish to broaden their knowledge in the field of pulmonary atelectasis.

PATHOLOGIE UND KLINIK IN EINZELDARSTELLUNGEN. BAND 8. KLINIK DER SUBAKUTEN BAKTERIELLEN ENDOCARDITIS. By Frank Schaub, Oberärzt der Medizinischen Universitätsklinik, Zurich. Berlin, 1960, Springer Verlag, 207 pages. Price: DM 49, 60.

This is a new German-language monograph on subacute bacterial endocarditis by a Swiss clinician from the university medical clinic in Zurich. It includes a review of the literature as well as an analysis of a personally collected series of 172 cases from the author's own and several other Swiss hospitals. Principal emphasis is given to

clinical features of the disease and to treatment. There are also short but adequate accounts of bacteriology and pathologic anatomy. The book is well printed, and free use is made of tables (of which there are 38) for presentation of relevant statistical data.

To the American physician who reads German, Dr. Schaub's monograph offers a comprehensive review of this disease, and can be recommended as such. However, this is also true of Kerr's monograph in English. The advantages of the newer work are in the providing of more up-to-date details of treatment, and in the careful analysis of a well-studied large series of recent cases. Perhaps the most important feature of Schaub's work for American readers, and especially for libraries, lies in the abundant references to Continental literature; the reviewer counted 132 for the postwar years. A very interesting change during this time in Europe was the large number of culture-negative cases which appeared in several series, as compared with prewar experience. This sudden increase under disrupted living conditions is strongly suggestive of a different and even contagious causative organism. At least one German worker was led to suspect a viral etiology for these cases. Could many have been examples of the rickettsial subacute bacterial endocarditis of Q-fever described recently in *The Lancet*? The therapeutic implications of this question are very important.

UNTERSUCHUNG UND BEURTEILUNG DES HERZKRANKEN. By Prof. Dr. h.c. W. H. Knipping, Direktor der Med. Univ.-Klinik, Cologne; and Prof. Dr. W. Bolt, Doz. Dr. H. Valentin, and Doz. Dr. H. Venrath, Oberärzte an d. Med. Univ.-Klinik, Cologne. Second edition, Stuttgart, 1960, Ferdinand Enke Verlag, 638 pages, 390 illustrations, 25 tables. Price DM: 98.

The first edition of this work (1955) was reviewed in the *American Heart Journal* 51:645, 1956: "This is an up-to-date textbook on the diagnosis of heart disease, including catheterization, x-ray kymography, gas analysis and oximetry, angiography, electrocardiography and exercise tolerance tests." The second edition has been enlarged (about fifty per cent), documenting the progress in the diagnosis of heart disease over the past five years. The functional approach, particularly the spirographic analysis in exercise tolerance tests, is emphasized. Right and left ventricular insufficiency, pulmonary insufficiency, and combined insufficiency are differentiated with this method. Hemodynamic changes before, during, and after cardiac surgery are discussed in detail, including cardiac and respiratory arrest during operations. The equipment of a laboratory for diagnosis of heart disease is described in chapter "G" (pp. 417-446). At the time of the first edition the method of "Isotopen-Ansflutungs-Kurven," i.e., decay of radiation of Co^{60} stored in the myocardium, was in the initial phase of development; since then, much experience has been accumulated by the authors, and is presented in chapter "H" (pp. 447-461). Age has a significant effect on the speed of decay (slower in older people), and gross differences were found between infarcted and normal myocardium. This method holds much promise for the diagnosis of coronary heart disease, but is still in the phase of experimentation.

It is, of course, impossible to give equal representation to all methods which are used in the diagnosis of heart disease, without considerable enlargement of the book. Electrocardiography, for instance, cannot be adequately presented in 20 pages, nor ballistocardiography in 3 pages.

The authors go beyond the diagnosis of heart disease; questions of etiology and environmental factors are also considered, and particularly exercise therapy. Here, the experience of the authors is quite unique (extending over 30 years). Work tolerance is, of course, a fundamental consideration in the management of patients with heart disease, and the book provides much valuable information not easily obtainable elsewhere.

Announcement

A COURSE IN CARDIOLOGY (rheumatic fever, rheumatic heart disease, and congenital heart disease) for general physicians and specialists, sponsored by the Michigan Heart Association and the University of Michigan Medical Center, will be given March 13-17, 1961, at the University Hospital, Ann Arbor, Mich.

In addition to a number of eminent speakers from the state of Michigan, the following guest lecturers will participate: Richard J. Bing, M.D., Detroit; S. Gilbert Blount, M.D., Denver; Eugene W. Braunwald, M.D., Bethesda; Jesse E. Edwards, M.D., St. Paul; Earl B. Kay, M.D., Cleveland; John Kirklin, M.D., Rochester, Minn.; George Murphy, M.D., New York; Charles H. Rammelkamp, M.D., Cleveland; Will Sealy, M.D., Durham; Gene H. Stollerman, M.D., Chicago; and May G. Wilson, M.D., New York.

For further details, write to Dr. John M. Sheldon, Director, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.